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ETIOLOGY OF KAPOSI'S VARICELLIFORM ERUPTION

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KAPOSI'S varicelliform eruption is a comparatively rare exanthem occurring in patients with atopic eczema. The illness is characterized by high fever for from four to seven days, by leucopenia, and by the presence of umbilicated vesicles, some of which may become pustular. Only the eczematous portions of the skin are involved. The disease is self-limited, and in general the prognosis is good. However, fatalities do occur when acute encephalitis develops or in cases where superimposed bacterial infection of the skin is extensive. Bronchitis and bronchopneumonia are not uncommon complications and may be serious.

The condition was first described in detail by Kaposi[1] in 1887, who considered it an alarming complication of eczema infantum. The vesicles were described as lentil-sized, "filled with a clear serum, and the majority umbilicated." Kaposi classified the eruption as varicelliform, at the same time pointing out that eczema herpetiforme might be just as suitable a name. While nothing definite was stated as to etiology, it was suggested that the "epidermis loosened by eczema" might be "suitable soil" for the growth of a fungus or some other infectious agent.

In 1898 Juliusberg[2] described a fatal case diagnosed as Kaposi's varicelliform eruption. He noted the clinical similarity of the exanthem to those of variola and varicella but considered it a pyodermia. Since this time the cause of Kaposi's varicelliform eruption has been the subject of considerable discussion, a number of bacteria and the virus of vaccinia being implicated in various reports. Some authors have expressed the opinion that clinical differentiation between eczema vaccinatum, pustulosis varioliformis acuta, and Kaposi's varicelliform eruption is impossible, others that these conditions are entirely synonymous.[3-12] It is worthy of note that a number of workers have persisted in associating the virus of vaccinia with Kaposi's varicelliform eruption in spite of the fact that this exanthem has occurred in patients who had been vaccinated successfully against smallpox months or years previously, and in some instances successful vaccination was possible after recovery from Kaposi's varicelliform eruption.

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Thus confusion with regard to etiology has led to various attempts at isolation of an infectious agent.[13-17] Regardless of the fact that in many instances bacteria have been cultured from cutaneous lesions, the general consensus from the beginning has seemed to favor virus etiology. Of particular interest is the work of Brain and Lewis[18] who described a fatal case of Kaposi's varicelliform eruption and reported experimental findings. As the 15-year-old patient was unusually cooperative, an attempt was made at autoinoculation of material from fresh lesions into scarified noneczematous skin but without success. A supernatant derived from vesicular crusts emulsified in saline was inoculated intradermally into the plantar skin of guinea pigs. Repeated inoculation of this material resulted only in the isolation of *Streptococcus hemolyticus* and *Staphylococcus aureus*. Five rabbits gave positive results after corneal inoculation of vesicular fluid with the development of severe keratoconjunctivitis. Inclusion bodies could not be demonstrated, however, and further attempts at passage in rabbits were unsuccessful. Post-mortem skin material likewise gave negative results, and histologic studies of post-mortem skin revealed no inclusion bodies. Testicular inoculation in rabbits and serological tests against vaccinia virus were inconclusive.

Seidenberg[19] approached the problem of etiology in Kaposi's varicelliform eruption through a study of immunologic response in rabbits. Rabbits inoculated by cornea with pustular material from a patient diagnosed as a case of Kaposi's eruption were tested after recovery for immunity to vaccinia virus. All proved to be susceptible to inoculation with the virus of vaccinia but were completely immune to herpes virus. Seidenberg concluded that there is no cross immunity between the virus of vaccinia and the infectious agent of the eruption originally described by Kaposi.

Strickler[20] reported five cases of Kaposi's varicelliform eruption in children. Smears made from cutaneous lesions of these patients were examined for Paschen bodies and none was found. The Paul test was positive in one of the five. Attempts to isolate a virus by means of the chorioallantois yielded negative results.

Only recently, however, has the etiology been proved conclusively. While the present work was in progress, it came to our attention that Wenner[21] and Barton and Brunsting[22] working independently isolated strains of virus from cutaneous lesions of cases of Kaposi's varicelliform eruption, and in one case from brain tissue taken at the time of autopsy, which have been identified as belonging to the herpes group. In each instance primary isolation was accomplished by corneal inoculation in rabbits.

CASE REPORT AND EXPERIMENTAL FINDINGS

In January, 1944, a patient with Kaposi's varicelliform eruption was admitted to St. Louis Children's Hospital. Although certain clinical characteristics of this disease, for example, leucopenia accompanied by high fever and the appearance of the skin rash, had suggested a virus infection, up to that time no etiologic agent had been identified conclusively. With this in mind an attempt was made to isolate an infectious agent from the cutaneous lesions. The case history of this patient follows, together with the details of the experimental findings, a preliminary report of which was made in May, 1944.[23]

A. L., 15-month-old white male, was admitted to St. Louis Children's Hospital on Jan. 30, 1944, and was discharged on Feb. 13, 1944. At the time of admission his chief complaints were atopic eczema since the age of 6 weeks and an acute exanthem associated

with high fever for five days. The eczema which had begun on the cheeks at 6 weeks of age gradually spread to involve the antecubital and popliteal areas. On occasion the rash was noted on the neck and upper portion of the thorax. The severity of the eczema varied from time to time, dependent on season and therapy, but the skin was never completely clear at any time. The antecubital and popliteal spaces had never been completely free of the chronic skin irritation.

On Jan. 26, 1944, the mother noted that the child appeared drowsy and was unusually irritable. There was slight fever which rapidly rose to 40° C. Somewhat later that day the patient vomited. For the next five days the temperature remained elevated, ranging between 39° C. and 40° C. Associated with the onset of fever, a new rash consisting of macules from 1 to 2 mm. in diameter was noted on the child's cheeks. This rash soon spread involving the wrists, face, and neck. Within twenty-four hours the lesions became umbilicated vesicles which soon appeared pustular. Since the temperature failed to return

Fig. 1.—Cutaneous lesions.

to normal, and the skin rash seemed worse, the child was referred to St. Louis Children's Hospital for diagnosis and therapy. Diphtheria and whooping cough immunizations had been carried out, but the baby had never been vaccinated for smallpox. Aside from the eczema, the patient had not suffered any other illness, and mental and physical development was normal. The family history was of interest in that the mother as a girl had suffered occasionally from recurrent skin irritation, the nature of which was indefinite. The father had hives following tetanus antitoxin, suffers from intestinal upsets after ingestion of eggs, and sneezes when he comes in contact with clover and hay. There are no siblings, and no additional history of allergy was known in the family.

At the time of admission, the patient was a fairly well developed and nourished child appearing subacutely ill. The skin in the antecubital and popliteal spaces, on the dorsal surface of the hands, and about the neck, appeared thickened, slightly dry, and scaly. Superimposed on this chronic eczematous rash was the acute exanthem. The lesions consisted of papules, umbilicated vesicles, and umbilicated pustules, ranging in size from 2 to

10 mm. in diameter and scattered over the involved skin in no definite arrangement (Fig. 1). The anterior and posterior cervical and the inguinal lymph nodes were enlarged. The mucous membranes were free of any eruption. Temperature at the time of admission was 40° C. (Fig. 2).

Therapy was as follows: Diet—soya formula, oatmeal, carrots, beets, peaches, beef, lamb, cevitamic acid, and Drisdol. Local therapy consisted of 4 per cent boric acid ointment, later Lassar's paste. Because of the high fever, the patient was placed on sulfadiazine, 0.5 Gm. every six hours (0.2 Gm. per kilogram per twenty-four hours). In two days this dosage was reduced to 0.25 Gm. every six hours (0.1 Gm. per kilogram per twenty-four hours). Chemotherapy was discontinued on the fourth hospital day. Within twenty-four hours the temperature had reached normal, and the baby appeared improved. The skin lesions showed definite signs of healing. Many of the older lesions were drying, and the newer lesions were progressing into the vesicular and pustular stages. For four days fresh lesions continued to appear. After one week's hospitalization, the skin lesions were much improved.

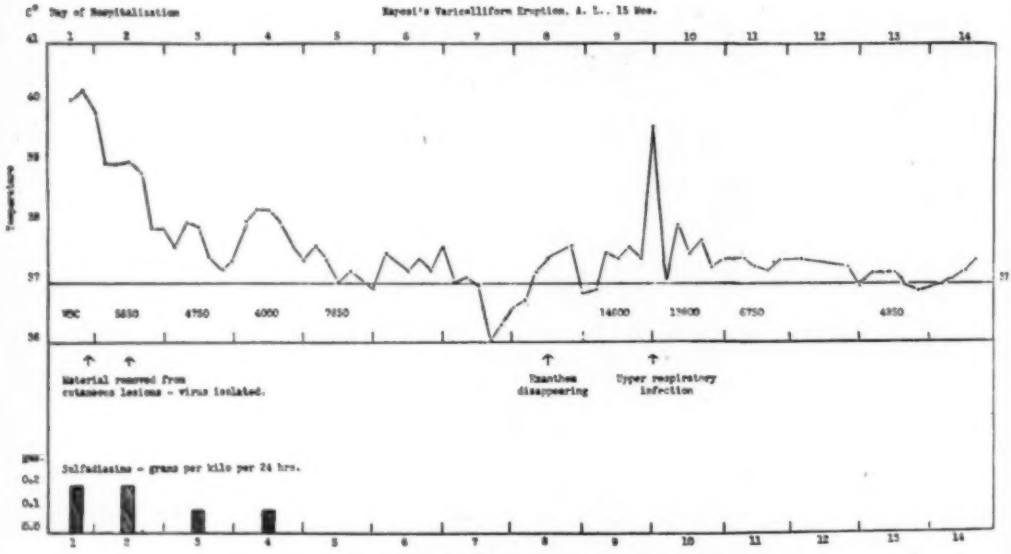

Fig. 2.—Chart of clinical course during hospital stay.

Toward the close of the ninth hospital day, the patient suddenly spiked a temperature of 39.7° C. On physical examination it was found that the throat was diffusely reddened; there was some mucopurulent discharge in the nasal passages. Diagnosis of acute respiratory infection was made. There was no re-exacerbation of the acute exanthem or of the eczema. In eight hours the temperature was normal, and the patient seemed quite well.

Laboratory work was of interest in that there was a persistent leucopenia, ranging from 4,000 to 7,000 cells. When the upper respiratory infection occurred, the white blood cell count reached 14,000. Five days later it was again 4,850. Aside from eosinophilia, 4 per cent, and a moderate shift to the left, there was nothing unusual about the blood picture. Urinalysis and Wassermann test were negative. Culture of the skin lesions on two occasions gave a heavy growth of *Staph. aureus* and *Str. hemolyticus*. Blood culture taken on admission was sterile. A biopsy of the skin was obtained on the tenth hospital day. The patient was discharged on the fourteenth hospital day in excellent condition. The exanthematous lesions had cleared completely, and the infantile eczema was less marked than it had been for a long time.

EXPERIMENTAL FINDINGS

Fluid removed from cutaneous vesicles on the fifth and sixth days of illness was cultured by routine bacteriologic methods, pure cultures of *Str. hemolyticus* and *Staph. aureus* resulting. At the same time material from these

cutaneous vesicles was inoculated on the scarified cornea of a rabbit. Within three days lesions were noted. On the fourth day the rabbit cornea was removed, washed in sterile saline, and triturated in tryptose-phosphate broth in an agate mortar. After centrifugation, the supernatant fluid was Seitz-filtered and inoculated into mice intracerebrally and onto the retracted chorioallantois of embryonated hen's eggs. Blood agar cultures of the inocula, aerobic and microaerophilic, were sterile. The mice so inoculated developed convulsions and died in from two to four days, and by the fourth day numerous small, pocklike lesions were observed on the chorioallantoic membranes. The strain has been perpetuated readily by egg and mouse passage. Other samples of vesicular fluid inoculated directly onto the retracted chorioallantoic membrane produced small pocklike lesions in from four to five days. There was no evidence of bacterial infection, and all cultures on blood agar were consistently negative. The egg strain has been maintained in serial passage on the chorioallantois, and transfer from eggs to mice and to rabbit's cornea gave results identical with the foregoing.

The two strains of virus, one isolated primarily by means of the rabbit's cornea and the other isolated primarily on the chorioallantoic membrane, gave similar results in all studies. Both strains have been well established in mice. Intracerebral inoculation of the virus in mice produces convulsions and death in from two to seven days in dilutions of 10^{-1} through 10^{-5}. Detailed titration studies have shown the virus unusually infective for mice: at 10^{-8} all mice die in from eight to nine days; at 10^{-9} and 10^{-10} approximately one-half die in ten days; and at 10^{-11} a few die in ten and eleven days.

The infectious agent is filtrable—Berkefeld "fine" V-13 and N filters.

Mice are susceptible to the virus by other portals of entry: by the intraperitoneal route mice die in convulsions in from six to eight days, by intranasal in seven to ten days, and by skin scarification in from seven to twelve days. The virus in each instance was isolated readily from the brain.

Intracerebral inoculation in hamsters produced convulsions and death in from four to five days, and hamsters inoculated by skin scarification died eight to ten days later. Recovery of virus from the brain was accomplished.

Rabbits inoculated by cornea in the usual manner were observed for signs of encephalitis. By the ninth to eleventh day central nervous system signs were marked—hyperirritability, tremors, circular movements, extreme photophobia, and convulsions. Death occurred between the twelfth and fourteenth days. Rabbits inoculated intracerebrally showed signs of encephalitis in five to six days and died in seven to nine days.

IDENTIFICATION OF VIRUS

In order to ascertain whether the patient was developing increasing antibody titer against the virus isolated from the cutaneous lesions, mouse protection tests (serum-virus neutralization) were made with serum samples taken at seven, fifteen, seventeen, and thirty days after onset of the exanthem. It will be noted from the results given in Table I that the patient developed type-specific antibodies to the newly isolated infectious agent during the course of clinical recovery. Microscopic section of brain from mice developing convulsions at varying intervals following intracerebral inoculation revealed the presence of a diffuse encephalitic process. Acidophilic intranuclear inclusion bodies were seen. The general pathologic picture and the occurrence of these inclusion bodies strongly suggested a herpetic infection.

Likewise lesions produced on the chorioallantoic membrane were similar to those associated with herpes virus. Grossly the lesions are small, discrete and opaque (Fig. 3). Microscopic section of the chorioallantois shows cellular proliferation in the ectodermal layer, marked cellular proliferation in the mesoderm with considerable cellular infiltration and a slight proliferation in the endodermal layer. Acidophilic intranuclear inclusion bodies were present.

In the rabbit's cornea visible changes occur within three days after inoculation, minute slightly elevated opacities appearing at the site of scarification. Microscopic section revealed considerable epithelial cell proliferation in the cornea, and again intranuclear inclusion bodies were noted.

Skin biopsy from the patient showed chronic inflammatory process with no characteristic viral pathologic change.

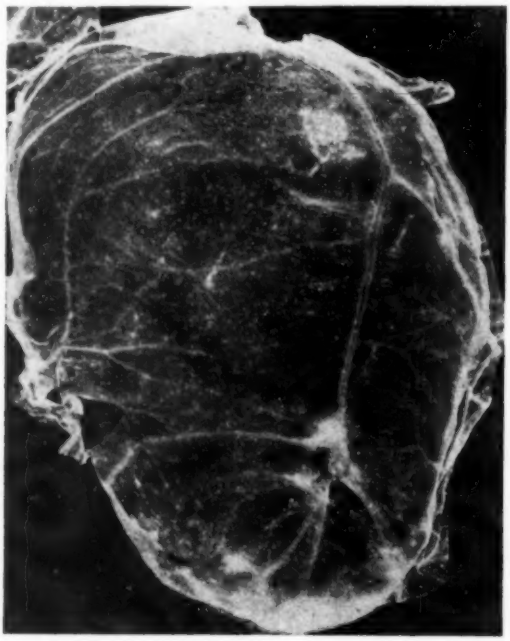

Fig. 3.—Showing type of lesion on the chorioallantoic membrane.

Since these observations suggested that the infectious agent is a virus of the herpes group, protection tests were repeated in order to ascertain whether the serum samples of the patient showed increasing antibody titer to a known strain of herpes as well as to the newly isolated virus. Accordingly, parallel mouse protection tests were carried out simultaneously using serum samples with corresponding dilutions of the unknown virus and of a known herpes simplex (HF strain, Rockefeller). The results of these two series which are shown in Table II are strikingly coincident. With the exception of one death in 10^{-4}, serum I, on the ninth day, and its corresponding survival in the herpes series, and one death by trauma in 10^{-3}, serum III, herpes series, they are identical.

Passive-transfer egg protection tests performed with the two strains of virus simultaneously using again the same serum samples gave similar findings.

Furthermore, cross-protection was demonstrated between the newly isolated virus and a known hyperimmune herpes serum.

Since vaccinia has been implicated in a number of published reports, egg protection tests[24] were made using a known vaccinia and the serum samples of the patient. No evidence of vaccinia antibody was demonstrated in any of the serum samples.

Table I. Mouse Protection Test (Serum-Virus Mixtures) Showing Increasing Titre of Humoral Antibody to Newly Isolated Virus during Course of the Illness

Dilutions of Virus	Patient's Serum I 7 days after onset	Patient's Serum III 15 days after onset	Patient's Serum IV 17 days after onset	Patient's Serum V 30 days after onset	Control Broth	Normal Human Serum
10^{-2}	(4) (4) / (5) (7)	□ □ / □ □	(T) (10) / □ □	(T) □ / □ □	(3) (3) / (3) (3)	(4) (4) / (4) (5)
10^{-3}	(7) (7) / (7) (7)	□ □ / □ □	□ □ / □ □	□ □ / □ □	(4) (4) / (4) (4)	(5) (5) / (5) (5)
10^{-4}	(6) (7) / □ □	□ □ / □ □	□ □ / □ □	(T) □ / □ □	(4) (4) / (5) (5)	(7) (7) / (7) (8)
10^{-5}	□ □ / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	(5) (5) / (6) (7)	(8) (8) / (8) (8)

□ = Survived T = Died trauma

(○) = Died in convulsions, figure within circle indicating day of death

Table II. Mouse Protection Test Showing Similar Increasing Titre of Humoral Antibody to Newly Isolated Virus and to Herpes Virus (HF Strain).

	Patient's Serum I Virus Isol. from Patient	Patient's Serum III Virus Isol. from Patient	Patient's Serum IV Virus Isol. from Patient	Patient's Serum V Virus Isol. from Patient	Patient's Serum I Herpes Virus	Patient's Serum III Herpes Virus	Patient's Serum IV Herpes Virus	Patient's Serum V Herpes Virus	Control Broth
10^{-2}	(4) (4) / (4) (4)	□ □ / □ □	□ (T) / □ □	□ □ / □ □	(4) (4) / (5) (4)	□ □ / □ □	□ □ / (T) □	□ □ / □ □	(3) (3) / (4) (3)
10^{-3}	(5) (5) / (5) (6)	□ □ / □ □	□ □ / □ □	□ □ / □ □	(5) (5) / (5) (6)	□ □ / (T) □	□ □ / □ □	□ □ / □ □	(3) (4) / (4) (4)
10^{-4}	(6) (6) / (9) □	□ □ / □ □	□ □ / □ □	□ □ / □ □	(6) (7) / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	(4) (5) / (5) (5)
10^{-5}	□ □ / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	□ □ / □ □	(6) (7) / (7) (9)

□ = Survived T = Died trauma

(○) = Died in convulsions, figure within circle indicating day of death

Blood specimens obtained from five other cases, four from Drs. Clinton W. Lane and Walter C. Herold, St. Louis, one from Dr. Stanley Gibson, Chicago, were tested for the presence of immune bodies against the newly isolated virus and against the HF herpes strain. None of these cases was seen by us personally, and in no instance were we able to test blood samples taken early as well as late in the clinical course of the disease. Only serum samples obtained late in the illness or at considerable time after recovery were available. Dr. Gibson's case and two of the Lane and Herold cases showed significant antibody titer to the Kaposi's virus and to the HF herpes strain. The remaining two cases of Lane and Herold failed to show a significant level of antibody against either the Kaposi's virus or the known herpes virus. These authors[25] offer the following explanation of the apparent discrepancy. One of the patients did not show all of the characteristics typical of Kaposi's varicelliform eruption, but had been considered "a pyodermia superimposed on a disseminated neurodermatitis." The blood sample was submitted along with the others for comparison and verification of diagnosis. Lack of antibody in the other case, which had presented a typical picture of Kaposi's varicelliform eruption, was interpreted by Lane and Herold[25]—"in two ways: In this particular case the disease may have been produced by a virus unrelated"—to the strains of virus employed in the tests—"or in the intervening twelve months since recovery the antibodies may have disappeared from the serum. A loss of this character has been recorded by Wenner."

SUMMARY

A filtrable virus (Berkefeld V-13 "fine" and N filters) isolated from the skin lesions of a 15-month-old child, showing a clinical picture typical of Kaposi's varicelliform eruption, was identified as a member of the herpes group. It is noteworthy that the virus was isolated not only by means of the rabbit's cornea but also directly on the chorioallantois of the developing hen's egg. The latter finding would seem to exclude any possibility that a latent herpes virus might have been reinactivated in the rabbit by experimental manipulation.

While these investigations were in progress, it came to our attention that strains of herpes were isolated and identified in two other laboratories by Wenner[21] and by Barton and Brunsting,[22] working independently.

It seems logical to conclude that a strain of herpes virus is the etiologic agent involved in at least some of the cases diagnosed as Kaposi's varicelliform eruption.

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REFERENCES

1. Kaposi, M. J.: Pathologie und Therapie der Hautkrankheiten, Berlin, 1887, Urban & Schwarzenberg; ed. 2, 1889; Also, Diseases of Skin, New York, 1895, William Wood & Company.
2. Juliusberg, F.: Arch. f. Dermat. u. Syph. 46: 21, 1898.
3. Ellis, F. A.: J. A. M. A. 104: 1891, 1935.
4. Corson, E. F., and Ludy, J. B.: Am. J. Dis. Child. 50: 1476, 1935.
5. Goeckerman, W. H., and Wilhelm, L. F. X.: Arch. Dermat. & Syph. 32: 59, 1935.
6. McLachlan, A. D., and Gillespie, M.: Brit. J. Dermat. 48: 337, 1936.
7. Tedder, J. W.: Arch. Dermat. & Syph. 34: 1008, 1936.
8. Schwartz, W. F.: Arch. Dermat. & Syph. 39: 173, 1939.
9. King, A. D.: Arch. Dermat. & Syph. 39: 1035, 1939.

10. Ronchese, F.: Arch. Dermat. & Syph. 47: 613, 1943.
11. Brown, E. L.: Arch. Pediat. 61: 233, 1944.
12. Connor, A., and Gonce, J. E.: J. PEDIAT. 23: 335, 1943.
13. Freud, P.: Monatschr. f. Kinderh. 51: 28, 1931.
14. Freund, H.: Dermat. Wchnschr. 98: 52, 1934.
15. Frühwald, R.: Dermat. Wchnschr. 99: 922, 1934.
16. Bentley, F. R.: Brit. J. Dermat. 52: 222, 1940.
17. Platou, E. S.: Am. J. Dis. Child. 48: 333, 1934.
18. Brain, R. L., and Lewis, B.: Brit. J. Dermat. 49: 551, 1937.
19. Seidenberg, S.: Schweiz. Ztschr. f. Path. u. Bakt. 4: 398, 1941.
20. Strickler, A.: Urol. & Cutan. Rev. 48: 340, 1944.
21. Wenner, H. A.: Am. J. Dis. Child. 67: 247, 1944.
22. Barton, R. L., and Brunsting, L. A.: Proc. Staff Meet., Mayo Clin. 18: 199, 1943; Arch. Dermat. & Syph. 50: 99, 1944.
23. Blattner, R. J., Heys, F. M., and Harrison, M. L. K.: Science 99: 432, 1944.
24. Blattner, R. J., Heys, F. M., and Gollub, S. W.: J. Immunol. 46: 207, 1943.
25. Lane, C. W., and Herold, W. C.: Arch. Dermat. & Syph. 50: 396, 1944.

GROWTH CHARTS FOR USE IN PEDIATRIC PRACTICE

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INTRODUCTION

GROWTH is a manifestation of life in the young and its rate and quality are importantly related to the general health and welfare of the individual. Because of this important relationship, the pediatrist must have intimate knowledge of the phenomenon of growth. It is an accepted practice in pediatrics to obtain height and weight measurements as a part of the routine physical examination. If these figures are accurate and obtained over a period of time for a given child, his pattern of growth under a given regimen of living will become known. One will also have a fair index to the build of the individual he is observing. In periods of very rapid growth when the organism is under metabolic stress, such as infancy and the prepuberal spurt, the probability of nutritional imbalance is great. However, at all ages nutritional deficiencies would more likely be recognized in their incipiency if an accurate record of the child's growth is kept and appraised. Further, with nearly every disease process there is some impairment of growth and consequently the proper interpretation of height and weight values may make possible early recognition of a disease and continued observation may give a good index as to the success of therapy. To expedite evaluation it is helpful for the experienced observer, and necessary for the inexperienced, to have a graph showing the norms of growth for infants and children. We felt that it should be possible to devise a simple, yet reasonably complete graph that could be easily understood by the physician, medical student and nurse, and meaningful even to the nonprofessional person.

HISTORICAL BACKGROUND

The fundamental relationship between the height and weight and the proportions of the human body have been studied and reported for a long time. Quetelet[1] made one of the first scientific studies of growth (1836). Wood[2] (1918) using data on boys and girls enrolled in several schools in the

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east and midwest United States presented tables of average weight for height for boys and girls. The next decade Wood and Baldwin[3] revised these tables to present mean weight for sex-age-height groups. Woodbury[4] (1921) compiled weight norms for sex-age-height groups of children at ages between birth and six years. The Baldwin-Wood and Woodbury tables have been widely used. For the most part they have been used to appraise physical status or nutrition at a given time. There has not been agreement regarding these norms, or others that have appeared in the last two decades, on the manner in which evaluations should be made. Among those who have used the norms there has been appreciable difference of opinion concerning the amount a child could deviate from the average before he should be considered abnormally overweight or underweight for his sex, height, and age. Kornfeld[5] (1929) compiled standards for height and weight for boys and for girls from birth to 20 years of age using subjects of Northern European origin. Burgess[6] (1937) using data compiled on American-born children, published height charts showing height curves for various percentile levels at given ages. Norms presented in terms of curves have a decided advantage over tables, for when an individual's measurements are plotted on such a growth chart one has a simple graphic picture of his physical status and progress in the particular trait under study. The evaluation that one makes is that a given child stands at a certain percentile level relative to a large group of children of his own age, and his progress from measurement to measurement can be appraised by comparing it with the pattern of growth shown by the curve of the chart and by reference to his previous record. Wetzel[7] (1943), through his grid for evaluating physical fitness, has made a distinct contribution to the interpretation of physical measurements of height and weight in that he has stressed to the clinician the importance of following the child's progress in height and weight. While he has not elaborated the assumptions and procedures employed in constructing his chart he has illustrated its practical application. It is, however, disconcerting for the physician to use a chart that is not clearly understood.

Stuart[8] (1934) and Vickers and Stuart[9] (1943) have recognized the place of anthropometry in the practice of pediatrics and have stressed standardization and accuracy of the anthropometrical measurements if they are to be a helpful part of the child's physical examination.

Boyd[10, 11] (1941 and 1944) has emphasized the necessity of careful observation of the growth of the child and believes that satisfactory or unsatisfactory growth is a very important sign in diagnosing or evaluating a child's condition. He says, "The child's poor growth may offer the first or even the only clinical evidence that abnormality is present." He is of the opinion that the substandard growth of the child is dismissed too frequently with the explanation that such growth is characteristic of his family and consequently no effort is made to seek a cause or explanation in the child's environment. Referring to the child's physical examination he says, "The status of the physique frequently is not subjected to any verification or comparison with average standards. Only when deviations from the usual physique are excessive or when they comprise the entrance complaint, is it customary for the physician to direct his attention toward such careful appraisal."

CHARTS

Charts of height-age and weight-age for boys and for girls have been constructed at the University of Iowa for clinical use by the Department of Pedi-

atrics and State Services for Crippled Children (Figs. 1 to 7). The data on which these charts are based are 13,500 height and 11,100 weight observations of Iowa City boys and girls enrolled in the University well-infant laboratory, preschool laboratories, elementary school, and high school between 1920 and 1940. The measurements were made by the physical growth staff of the Iowa Child Welfare Research Station. The majority of the 1,500 boys and 1,500

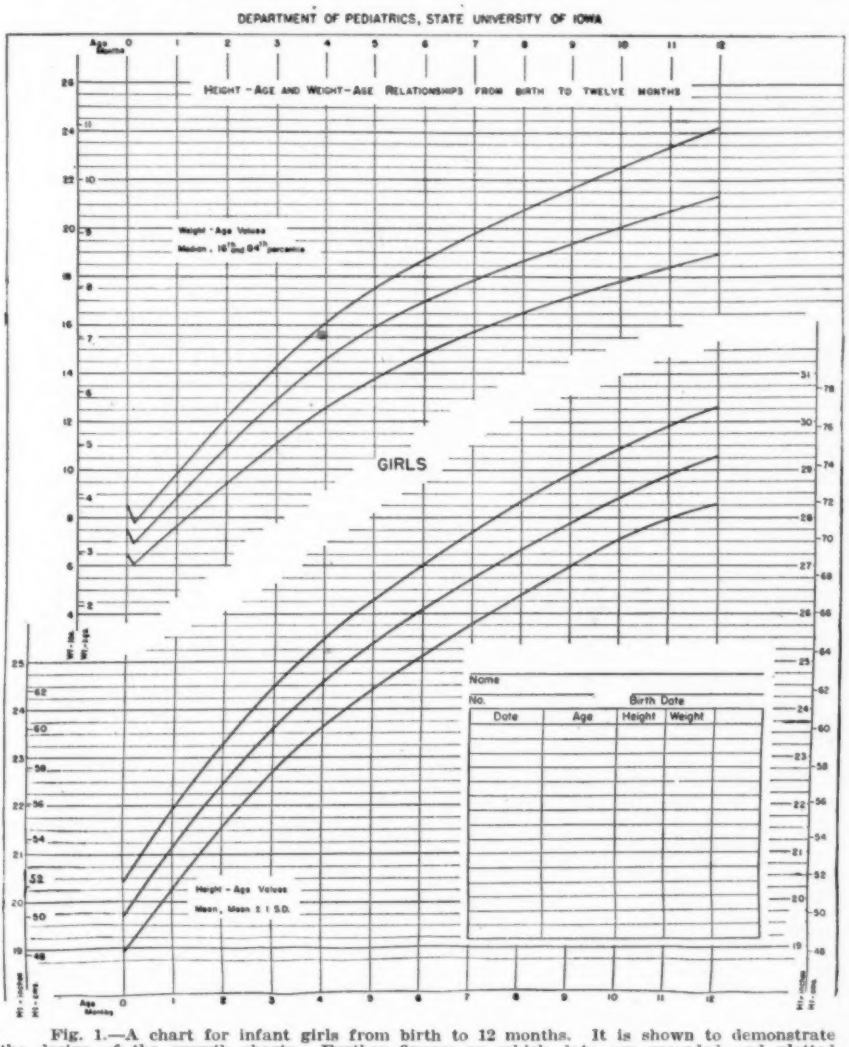

Fig. 1.—A chart for infant girls from birth to 12 months. It is shown to demonstrate the design of the growth charts. Further figures on which data are recorded and plotted show the other five charts slightly modified for publication.

girls came from the higher socioeconomic group. The infant data are the heights and weights of infants born in the community of Iowa City from 1926 to 1940 and observed in the well-infant laboratory. The mothers of many of these babies had the advantage of professional nutritional guidance. The only exception to these sources are the data on newborn babies which were compiled from the literature on American white newborn boys and girls.[12-14]

The age ranges used for the charts for the infants, preschool and school children have been selected by trial and error in clinical practice. During infancy, which is a period of rapid growth and of frequent assessment of growth, the chart includes the first year of postnatal life with the age scale divided in monthly periods (Figs. 1, 2, 3). The chart for the preschool child is given for the first six years of postnatal growth with the age scale divided

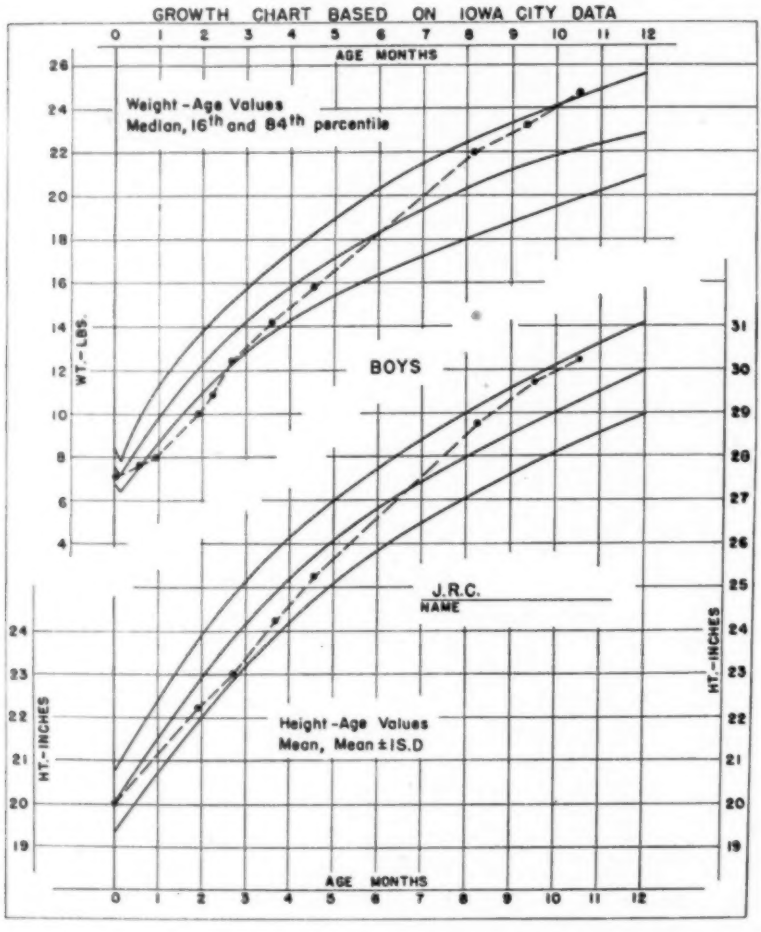

Fig. 2.—A growth chart for infant boys on which are plotted the curves of the height and the weight of J. R. C. His parents, overanxious, did not adhere strictly to any feeding schedule until he was 2 months old. The baby's progress was unsatisfactory during this period. Later when good pediatric care was given, the child gained well and showed compensatory growth.

into semiannual intervals (Figs. 4, 5). There is overlapping in the age range of the infant and preschool charts. It was found desirable to have the records for infancy plotted with the record for early childhood when circumstances make the former available. The chart for school children extends over the age range from 5 to 18 years (Figs. 6, 7). In the lower right position on the latter chart is given a scale showing a zone of rapid growth in height. The charts are printed on 11 by 8½ inch sheets of good quality paper and glued

in tablets of 100 copies. The top of each sheet is punched so it will fit neatly in the hospital medical history.

CURVES

On each chart there is a set of three curves for height and for weight (Fig. 1). The middle curve gives the average.* The outside curves for height

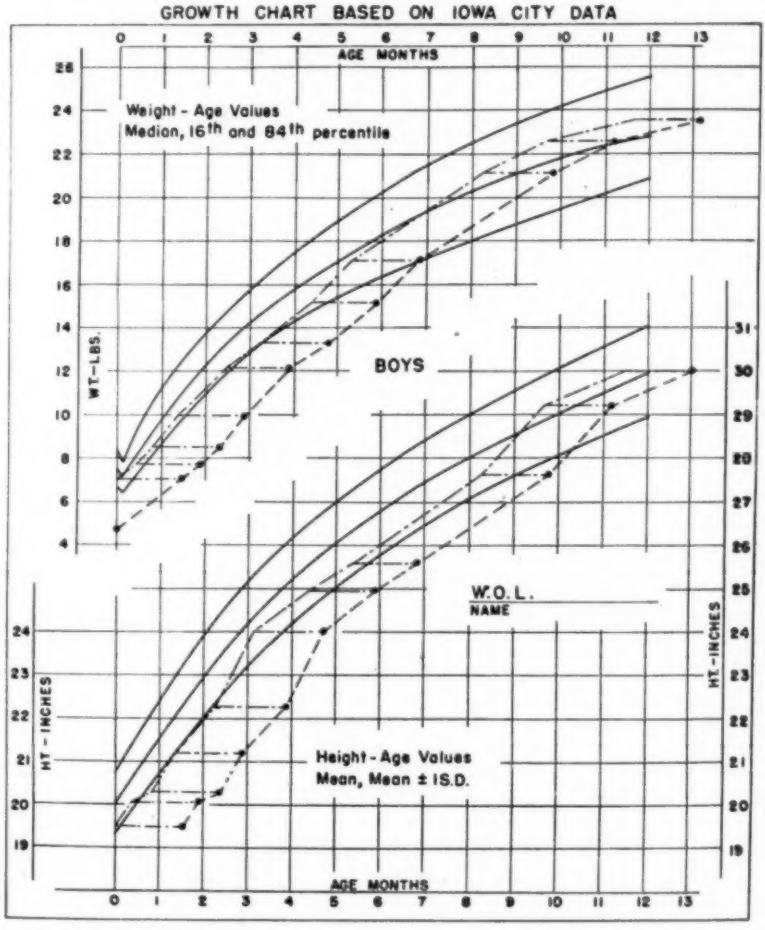

Fig. 3.—W. O. L. is an infant boy born about six weeks prematurely. The broken line with the dots shows his actual growth in relation to the norms of infant boys. The other broken line shows his growth curve adjusted for six weeks' prematurity. This baby was fed according to his developmental age rather than his birth age. He made excellent progress in height and weight. At the end of the first year he was receiving the feedings of an average infant the same chronological age. His growth chart was reassuring as to satisfactory progress and nutrition.

represent points on the height scale that are 1 standard deviation above the average and 1 standard deviation below the average. For weight the outside curves represent the values for the eighty-fourth and sixteenth percentiles and correspond to the values plus and minus one standard deviation of a normal distribution. Thus are given three levels of growth for height and for weight. If a child's growth in height follows along the upper curve he is ranking at

*Since height is normally distributed for age groups, we used the mean value and since weight is slightly skewed for age groups, we used the median (50th percentile).

the eighty-fourth percentile among his group of sex, age,* race, and geographic environment. If he is following the lower curve, he is ranking at the sixteenth percentile of his peers. In discussing these curves we use interchangeably the terms height curve and height-age curve, and weight curve and weight-age curve.

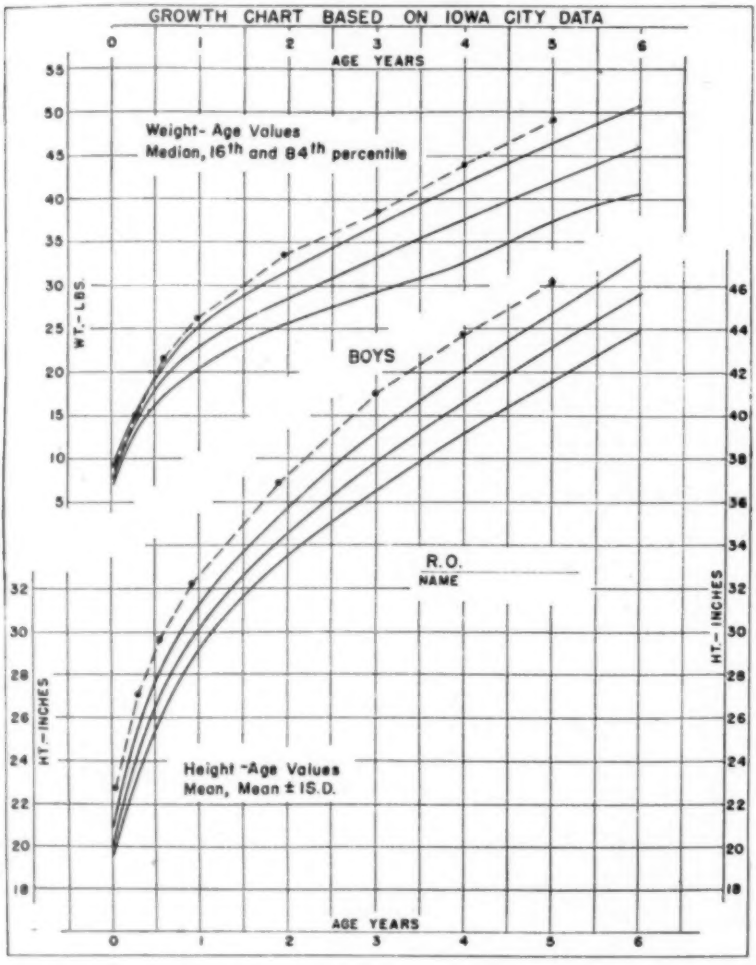

Fig. 4.—The heights and weights of R. O. are plotted on a growth chart for boys between 0 and 6 years. R. O., a well child, favored by environment, attended the University preschool where his physical measurements were observed regularly. His level of growth in height and weight for his age is high. His progress on the whole parallels the curve of the growth chart.

ZONE OF RAPID GROWTH (FIGS. 6, 7)

Two percentile values each have been selected to show the "beginning" and the "crest" of the adolescent acceleration in height. The first two percentiles mark the ages at which 16 and 50 per cent of each sex have begun

*In computing the mean, standard deviation, and percentiles for given age groups from 3 months to 5 years and 6 months, the range extends 30 days below the age given to 30 days above. For the school age children the age range extends from 6 months below the given age to six months above this age. The homogeneity of the age sample particularly affects the standard deviation and the extreme percentiles.

their acceleration. In determining these values the beginning of the "spurt" was noted on the individual height-age curves of 138 boys and 106 girls.* The last two percentile values mark the ages at which 50 and 84 per cent of each sex have reached the crest of their acceleration. These values were obtained from noting the crest of growth in the afore-mentioned individual height-age curves. Sixteen per cent of the boys had begun acceleration in height by 11 years, 8 months, and 50 per cent by 12 years, 11 months. The

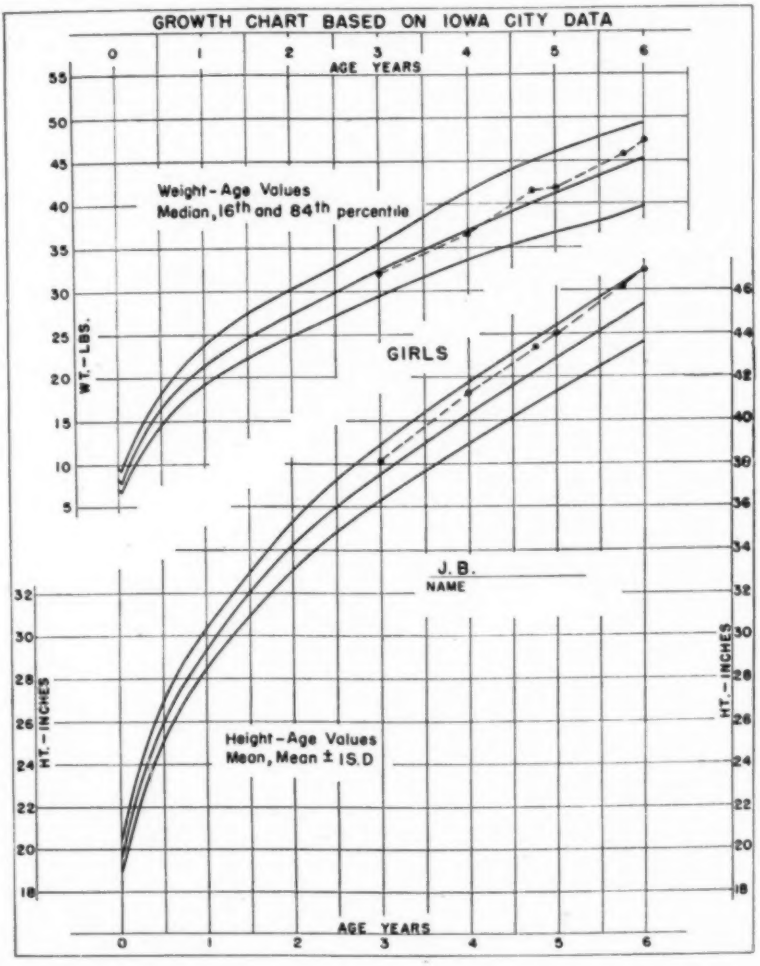

Fig. 5.—The heights and weights of J. B. are plotted on a growth chart for preschool girls. This well child attended the University laboratory school where her heights and weights were observed regularly. Her growth curves are slightly steeper than the norms and reveal very satisfactory progress during this period of observation.

crest of height growth was attained for 50 per cent of the boys by 14 years, 7 months, and 84 per cent by 15 years, 7 months. Sixteen per cent of the girls had begun acceleration in height by 9 years, 2 months, and 50 per cent by 10 years, 8 months. The crest of the height curve was attained for 50 per cent

*The statistics compiled on spurt of growth were based on the published data in the study, Meredith, Howard V.: Stature of Massachusetts Children of Northern European and Italian Ancestry, Am. J. Phys. Anthrop. 24: 301, 1939.

of the girls by 12 years and for 84 per cent by 13 years. Typically, girls experience their greatest annual height increment one year preceding the menarche.[15] Also with boys the spurt of growth in height is undoubtedly correlated with the development of the primary and secondary sexual characteristics. The exact relation is not known except that some of the secondary characteristics are present generally before the boy has his maximum height growth.[16]

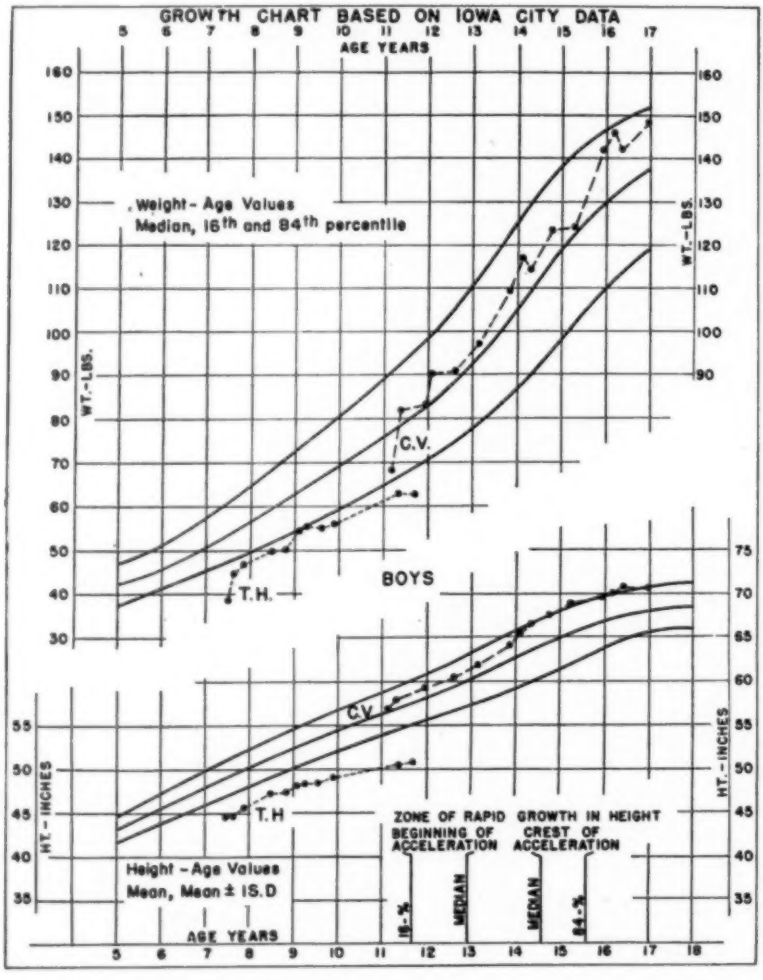

Fig. 6.—The curves of two diabetic boys are plotted on the growth chart for schoolboys. C. V. had his disease well controlled and made excellent progress. T. H. had his disease poorly controlled and made unsatisfactory progress.

CHARTING PROCEDURE

The name of the child, the hospital number, and the birth date are recorded in the place indicated on the chart. The date of examination, the height and the weight are recorded in the place indicated at each examination period. There are scales in English and metric units on both sides of the chart for height and for weight. As the guidelines correspond to the English units

it is easier to plot point values in the English units. The points plotted on the height-age curve correspond to the age and the height of the child at the time of examination. The points plotted on the weight-age curve correspond to the age and weight of the child at the time of examination.

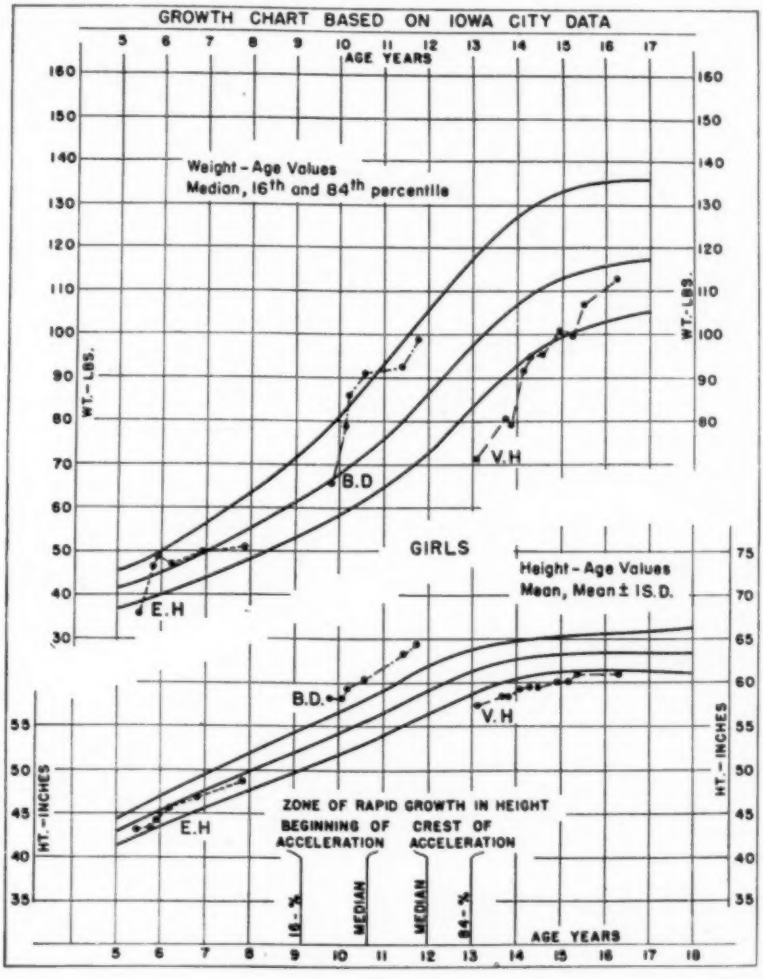

Fig. 7.—This is a growth chart for schoolgirls. The individual curves demonstrate the growth of three girls, E. H., B. D., and V. H. with rheumatic heart disease. With this disease the nutrition of the patient is very important. They were undernourished at the time of their original observation. Gains in height and weight were observed and were good indices as to the stage of the disease and the success of the therapy.

CLINICAL STUDIES

The following nine cases, taken from the files of the Department of Pediatrics and the Iowa Child Welfare Research Station, have been selected to illustrate some specific uses and interpretations of the growth charts. They reveal how closely related health and illness are to the growth of the child.

J. R. C. (Fig. 2) was an infant boy seen in the well-baby clinic. His height and weight are plotted on the infant boy's chart. He was brought to the clinic at the age of 2 months. At that time he was receiving an adequate diet but, because of the family, presented a

difficult problem of emotional adjustment. This infant was the only child of older over-anxious parents. They changed his feedings frequently and did not adhere strictly to any schedule. Under pediatric care, at 3 months of age the child showed compensatory growth and has continued to do so up to his last visit at the age of 10 months and 14 days. This child's weight and height measurements confirmed the inadequacy of the regimen followed during the first two months. His progress from two to ten months has been reassuring as to the adequacy of his care during this period.

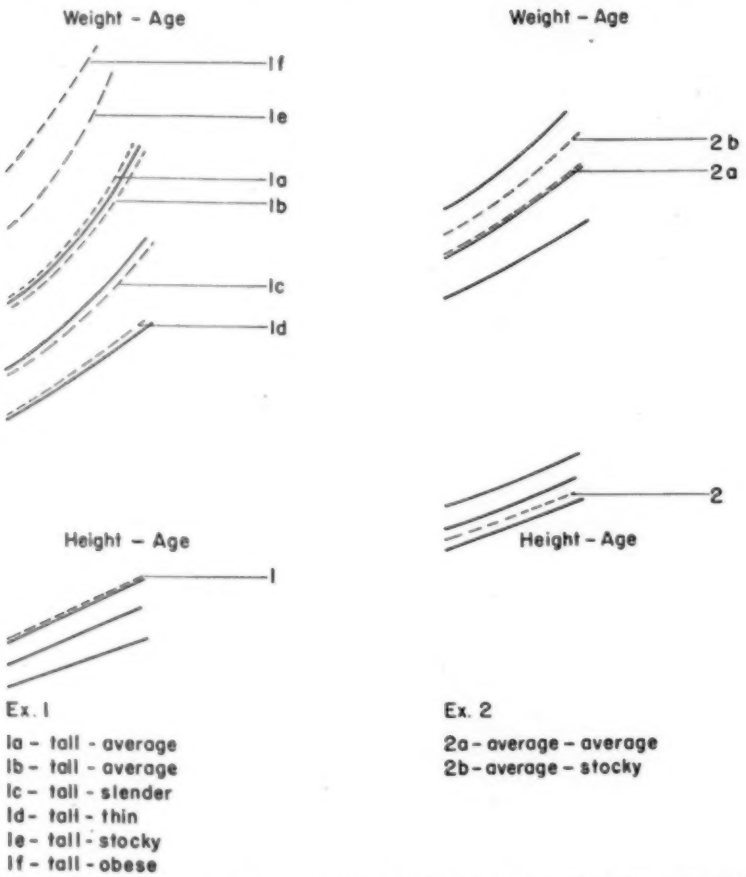

Fig. 8.—This chart illustrates the determination of build using segments of the growth charts for Examples 1 and 2.

W. O. L. (Fig. 3), an infant boy, has been seen frequently in the well-baby clinic since he was 6 weeks old. This baby was born about six weeks prematurely and was very small if compared to curves of growth for full-term infants. He has made excellent progress during the first postnatal year. In evaluating his status at each measuring period a better appraisal was obtained if the positions of the height curve and weight curve were extended back six weeks (as indicated on the chart). Special care was taken to feed this infant according to his developmental age rather than his birth age. However, the infant's progress, as shown by the chart, was accelerated and eventually his feedings were the same as for the average infant of the same chronological age.

The record of R. O. (Fig. 4) during his preschool years is plotted on the chart for boys from 0 to 6 years. This child was followed by the Iowa Child Welfare Research Station. Economically he was favored and his health and regimen of living were above

average. His father was tall and his mother was somewhat above average in height. His curve of height from 3 months to 5 years is well above the top curve of the chart and has proceeded in a regular manner at a rate similar in all respects to the growth chart. There are no dips in his weight curve.

J. B. (Fig. 5) was enrolled in the preschool and junior primary school of the University, where her height and weight were observed routinely. These heights and weights are plotted on the girl's chart for 0 to 6 years. Her chart demonstrates the growth of a healthy girl. Over the period from 3 to 6 years the relative position of the height and the weight curves is practically constant, that is, her curve of height relative to the mean curve of height is always proportionately higher than her curve of weight relative to the median curve of weight.

Fig. 6 is a chart showing the growth of two diabetic boys.

C. V. is a boy who has been known to have diabetes mellitus since he was 11 years old. His curves of height and weight are given on a boy's chart for ages 5 to 18 years (Fig. 6). This child has grown remarkably well despite the fact that he has moderately severe diabetes requiring about 70 units of insulin daily. His diabetes has remained under excellent control and his regimen of living is above average. At the period of the prepuberal spurt, his growth was apparently in no way inhibited and he made excellent progress. He has made good gains at all times and the irregularities in his weight curve are considered reflections of exercise and seasonal variations.

T. H. has been known to have diabetes mellitus since he was 7½ years old. His diabetes has been under poor control. Adverse living conditions have made it impossible to maintain an adequate diabetic regimen. His growth in height has been unsatisfactory.

Fig. 7 is a chart showing the growth of three girls who were observed in the cardiac service of the pediatric department.

CASE 1.—E. H. was a child of 5½ years of age who was admitted to the hospital with acute rheumatic fever and severe carditis. Height and weight could not be obtained until two weeks after admission because of her serious condition. The child was within the normal range for height for her age but was definitely underweight. The child's condition rapidly improved with treatment and she has remained well since. Her height and weight both show decided improvement.

CASE 2.—B. D. was a tall child of 9 years, 9 months of age who was admitted to the hospital with subacute rheumatic fever with minimal carditis. Although the child's weight was average for her age, she was decidedly underweight for her height. The patient's nutritional condition rapidly improved with good care as reflected by the chart. She has remained in good health and nutrition since that time.

CASE 3.—V. H. was a 13-year-old girl who was admitted to the hospital with chronic osteomyelitis and rheumatic heart disease. The child's nutrition was poor. She was short and underweight. Improvement of her nutritional state is reflected in the chart. Her rheumatic fever rapidly became inactive and her osteomyelitis is greatly improved.

DISCUSSION

To recognize the abnormal, one must know a great deal about the normal. Experience, of course, teaches much and is invaluable in interpretation. But frequently one seeks an objective way to evaluate the findings and a quantitative method of measuring and recording them. So it is that the pediatrist takes the height and weight of his patients in an effort to assess the growth of the child. The experienced physician may have a mental picture of the expected growth of a child of his race, sex, and age, and he may evaluate the child's measurements in terms of this picture. A much more accurate, objective, and reliable interpretation would be obtained if the child's measurements were plotted on a chart showing the mean and deviation of height and weight for different ages and the expected rates of growth. Once the measurements

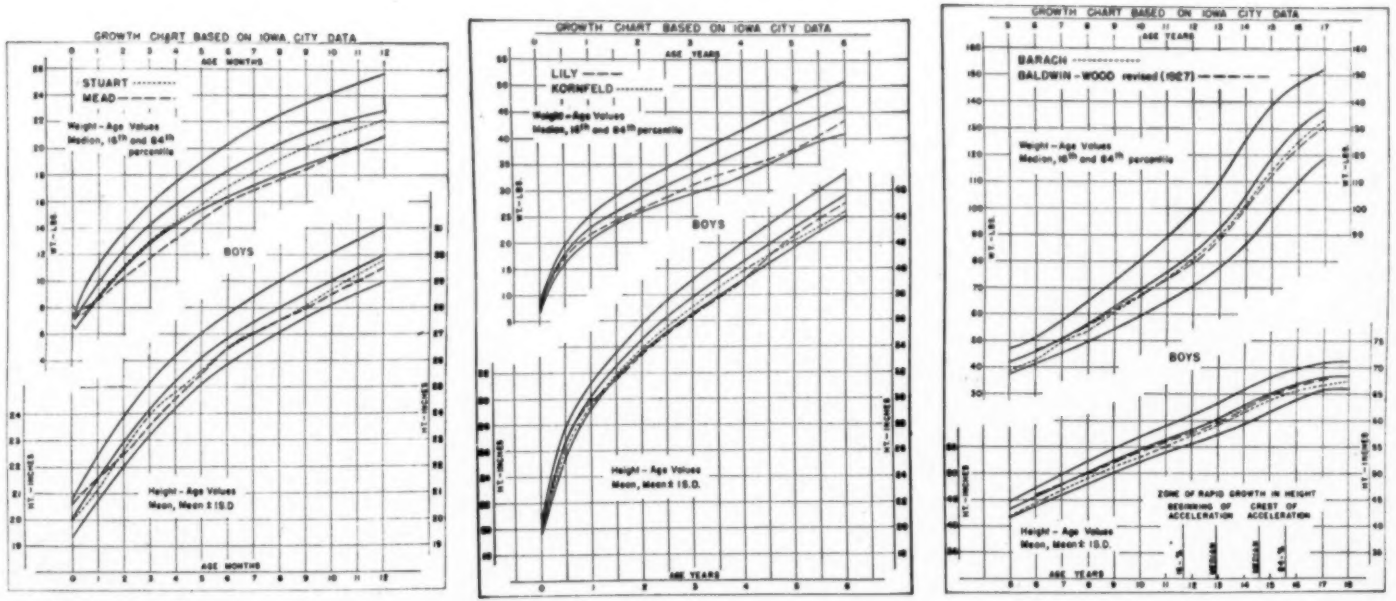

Fig. 9.—Superimposed on the charts of Iowa growth curves are comparable norms from other sources. The Iowa norms are as high as those of the other sources, or higher. The general pattern of the growth curves is similar for the different norms. The Iowa norms are considered good for pediatric practice because they represent a relatively high level of growth.

are plotted, one looks at a picture of growth with the intermediate numerical steps dispensed with once and for all. Patterns of growth of the individual are compared with the curves of the chart; levels of growth attained by the individual are examined in relation to the levels of the different percentiles of the growth chart. It is noted whether the curve tends to parallel those of the chart or whether it tends to deviate from the curves of the chart. These deviations then must be interpreted in the light of the medical and social history of the child and his physical examination.

The level of height and weight attained is important and meaningful when compared with norms. Among healthy normal children approximately two-thirds of the children will be found within the range of the two outer curves. It is rare to find healthy normal children two standard deviations above or below the mean height or weight for a given age.

The level of the height-age curve in relation to the level of the weight-age curve is an index of the build and also the nutrition of the child. When these curves have been obtained for a given child over a period of his life free from disease and from adverse environmental and dietary conditions, they indicate the general build of that child. However, when a disease entity or a markedly adverse environmental factor is present it is not possible to evaluate the true build of the child from observations made during this period. Either the build is determined from measurements observed prior to the onset of the disease or of the influence of adverse environment or from measurements observed after the disease has subsided or is controlled or the adverse environment rectified. For example, it is not possible to evaluate the true build of B. D. (Fig. 7). She was observed when her disease was active and for but a short period after her disease had subsided.

In classifying build we record (1) a rating for the child for his height-age; (2) a rating for his weight-age relative to his height-age. If the individual's height curve lies between the upper and lower curves of the growth chart he is classified average (A) height; if his height curve is on or above the upper curve of the chart he is classified tall (T); if his height curve is on or below the lower curve of the chart he is classified short (S). To classify the child as to whether he is slender, average, or stocky, we consider the relative positions of the individual's height-age and weight-age curves. In order to do this it is necessary to express the deviation of the individual curves from their respective norms in a common unit of measurement. A reasonable arbitrary unit is the standard deviation* of the distributions of height and of weight for age.† For simple practical use this is represented by the width of the space between the mid-line and the upper or lower lines of the chart.

To illustrate the procedure of classifying the build of individuals a few specific examples are given:

*A point 1 standard deviation from the mean is at the 84th percentile or the 16th percentile; a point 2 standard deviations from the mean is at the 98th or the 2nd percentile. These equivalents assume a normal distribution of the measurement for age. The distribution of weight for adolescent and postadolescent girls is slightly skewed and hence the differences between the median line and the upper line and between the median line and the lower line are unequal. In estimating build the width of the space in which the given curve falls is used as an approximate value of the standard deviation.

†The following is a more formal mathematical statement of the procedure for establishing whether the child is slender, average, or stocky. (1) Express the deviation of the individual's height curve from the average curve in units of standard deviations. (2) Express the deviation of the individual's weight curve from the average curve in units of standard deviations. (3) Determine algebraically (2) − (1). (4) A difference of 1 standard deviation or more is classified stocky; a difference of less than ±1 standard deviation is classified average; a difference of −1 standard deviation or more is slender.

Example 1.—If the height curve of an individual is just above the upper line of the height chart, then the child is classified as tall. The relationship of the weight curve of the child to his height curve is then considered. If his weight curve is also just above the upper line of the weight chart the child is classified tall-average (T-A) not tall-stocky (T-St). If the weight curve is just below the upper line the child would still be classified as tall-average (T-A) as the weight curve in relationship for the height curve is still within a standard deviation unit. If the weight curve for this individual is just below the mid-line then the child is classified tall-slender (T-Sl) and if the weight curve is still lower say near the lower line or below it is very likely that the child is not only slender but actually underweight (thin). If on the other hand the weight curve of the child were considerably above the upper weight curve of the chart, the child would be tall-stocky and greater degrees would mean that the child is not only stocky but actually obese (Fig. 8).

Example 2.—If the height curve of the child is one-half way between the middle and lower line of the height chart then he would be classified as average height. If the weight curve of this child is on the mid-line of the chart he is rated average so that his classification is average-average. If on the other hand the weight curve of this child is one-half way between the mid-line and the upper line of the weight chart he is classified average-stocky (A-St) because there is a difference of 1 standard deviation units in the relative positions of his height-age and weight-age curve (Fig. 8).

In assessing the nutrition from these charts the individual measurements are first evaluated in relation to the height-age chart as satisfactory or unsatisfactory in level and progress. If satisfactory, reference to the weight-age curve permits an evaluation as satisfactory or unsatisfactory in respect to whether the child is maintaining his established build and making normal progress. With unsatisfactory height-age, the weight-age may indicate satisfactory or unsatisfactory nutrition, but probably always warrants an investigation into the heredity, environment, history of disease, and quality of the diet.

Growth is primarily timed and partially controlled by the hormones of growth. The timing of the prepuberal spurt of growth in height is noteworthy. It should particularly enter into the evaluation of progress and development. The occurrence of the adolescent spurt in height indicates the onset of sexual maturation and foreshadows the approach of the cessation of linear growth.

So often in the past the norms available to the pediatrist have been based on a composite of data from sources none too well-described or of unknown heterogeneity. In using the Iowa data for these charts it is believed they give a standard of growth that approaches the optimum for general pediatric practice (Fig. 9). In devising these charts, an effort has been made to meet the needs of simplicity in design and interpretation. It is felt that these charts are meaningful to the nonprofessional as well as the professional person. Yet due to their simplicity it is easy for the professional person to relate the findings of these charts to other phases of growth and development which also are frequently expressed in terms of chronological age.

SUMMARY AND CONCLUSIONS

Six growth charts based on Iowa City data are presented with height-age and weight-age curves on each chart. A chart is given for each sex and for each of three age groupings, the infant (0 to 12 months); the preschool child (0 to 6 years); and the school child (5 to 18 years). These standards are considered to approach the optimum for general pediatric practice. This high level of growth accrues from the selection of subjects, most of whom were favored by environment. Special effort has been made to meet the needs of simplicity in design and interpretation of the growth charts so that they would be meaningful to the nonprofessional as well as the professional person.

We wish to acknowledge that many of the basic ideas in the designing of the charts were obtained from J. D. Boyd, M.D., and H. V. Meredith, Ph.D.; and also to express our indebtedness for their helpful suggestions in modifying and developing the charts.

REFERENCES

1. Quetelet, M. A.: Bachelier, Paris, 1836, Acad. roy. d. sc. d. lettr. et d. beaux-arts de Belg. 14: 138, 1847.
2. Wood, Thomas D.: Height and Weight Table for Girls and Boys, New York Child Health Organization, New York, 1918.
3. Wood, Thomas D.: The Child in School; Care of Its Health, The National Health Series, Funk and Wagnalls Company, 1924, pp. 52-53.
4. Woodbury, Robert M.: Statures and Weights of Children Under Six Years of Age, U. S. Dept. of Labor, Children's Bureau Pub. No. 87, 1921.
5. Kornfeld, W.: Ztschr. f. Kinderh. 48: 188, 1929.
6. Burgess, M. A.: J. Am. Statistical Assoc. 32: 290, 1937.
7. Wetzel, Norman C.: J. PEDIAT. 22: 82, 1943; J. PEDIAT. 22: 208, 1943.
8. Stuart, Harold C.: J. PEDIAT. 5: 194, 1934.
9. Vickers, Vernette S., and Stuart, Harold C.: J. PEDIAT. 22: 155, 1943.
10. Boyd, Julian D.: J. PEDIAT. 18: 289, 1941.
11. Boyd, Julian D.: J. Iowa State Med. Soc. 34: 61, 1944.
12. Meredith, H. V.: University of Iowa Studies, Studies in Child Welfare 11: 9, 1935.
13. Boynton, B.: University of Iowa Studies, Studies in Child Welfare 12: 8, 1936.
14. (a) Meredith, H. V.: Unpublished Revised Distributions of Height and Weight Measurements of Iowa City Children (1926-1940) From 3 Months to 24 Months; (b) Meredith, H. V., and Brown, A. W.: Human Biol. 11: 24, 1939; (c) Meredith, H. V.: University of Iowa Studies, Studies in Child Welfare 19: 44, 1943; (d) Holt, L. E., and Howland, John: Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., p. 13.
15. Simmons, Katherine, and Greulich, Walter: J. PEDIAT. 22: 518, 1943.
16. Jung, F. T.: Illinois M. J. 80: 477, 1941.

BONE GROWTH IN CONGENITAL MYXEDEMA

THE USE OF SERIAL ROENTGENOGRAMS OF THE OS RADIUS IN DIAGNOSIS AND REGULATION OF THERAPY DURING INFANCY

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THE chronologic appearance of centers for ossification is one of the most useful indices to thyroid function during infancy. Adequate standards for comparison are available, elaborate techniques and equipment are eliminated, and the method is based upon a fundamental action of the thyroid—orderly skeletal development. It is not, however, easily employed as a guide to the control of therapy in the young cretin since roentgenoscopically measurable changes occur too slowly to permit frequent reappraisal and regulation of dosage.‡ It has been our experience that certain findings in the shafts of long bones provide this information accurately.

Since continued development of osseous structures is dependent upon thyroxine, cessation of normal growth results when the infant is deprived of his supply. Such deficiency is reflected not only by failure of ossification

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‡The observations recorded deal only with infants born of mothers with normally functioning thyroids. The terms cretin and congenital myxedema are used interchangeably and advisedly.

centers to develop but also by marked decrease in the linear growth and calcification of the diaphyses. This can be determined radioscopically by comparison of the rate of extension with a normal curve and also by the appearance of a hard, densely calcified, epiphyseal plate. Administration of thyroid substance to a young cretin results in almost immediate resumption of bone growth and changes measurable by x-ray are visible within three weeks; the dense zone of calcification remains only as a scar and a distal band of new bone can be discerned.

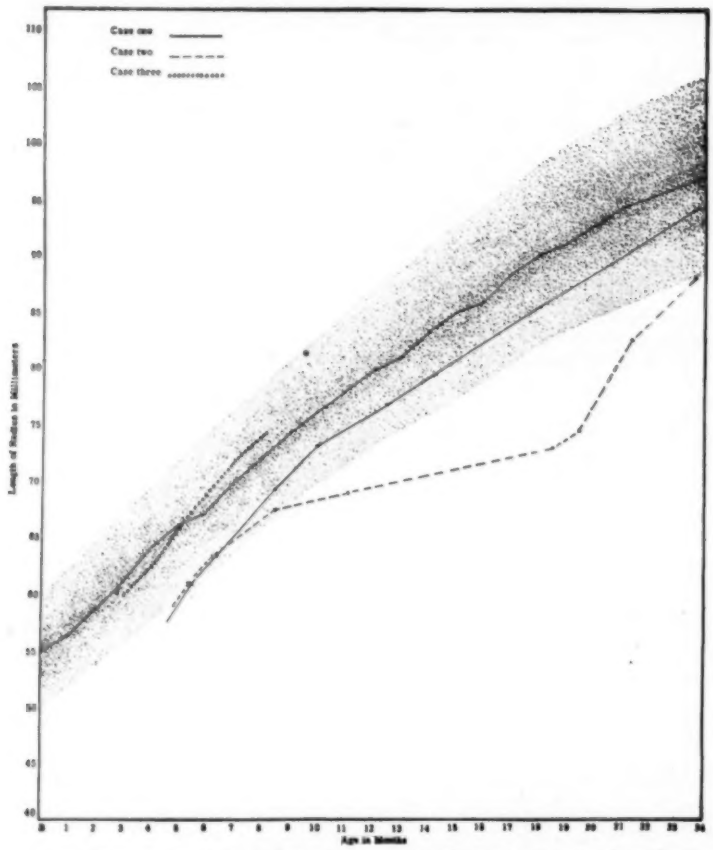


Fig. 1.—A normal curve for the growth of the radius during infancy and measurements on three patients with congenital myxedema.

The radius is ideally constituted for observing these changes since it is easily filmed and measured and since growth during the first two years takes place at a surprisingly constant rate. A curve, constructed from some four hundred measurements on the radii of babies without evidence of thyroid dysfunction, has been used as a standard* (Fig. 1). Five infants with congenital myxedema and a number with other disturbances in growth and development have been followed by serial roentgenograms of their radii and referred for comparison with this average curve. Results have been uniformly satisfactory

*We are extremely indebted to Dr. A. M. Washburn for furnishing linear measurements on his Denver study group. The remainder of the data are from the University of Oregon facilities. The shaded area in Fig. 1 encloses roughly plus and minus twice the standard deviation for the curve.

both in the diagnosis of athyreosis and in the regulation of therapy. The records of three cretins illustrate the value of long bone studies.

The first patient (Case 1, No. 123019) was a female born of normal parents and was seen by us at 4½ months of age. Nothing abnormal had been noted during the first two months of life but thereafter obstipation, irritability, and refusal of food appeared, conjunctive with the discontinuance of breast feedings. Abdominal distention became noticeable two weeks later and the severity of all symptoms increased until admission.* The mother had been aware that physical and mental development was not at the usual rate since about 3 months of age. The classic stigmata of cretinism were present and films showed absence of the carpal centers, a densely calcified epiphyseal plate, and radii far shorter than average (Fig. 2*A*). An immediate clinical response was obtained to the administration of 45 mg. of desiccated thyroid (Armour) daily.

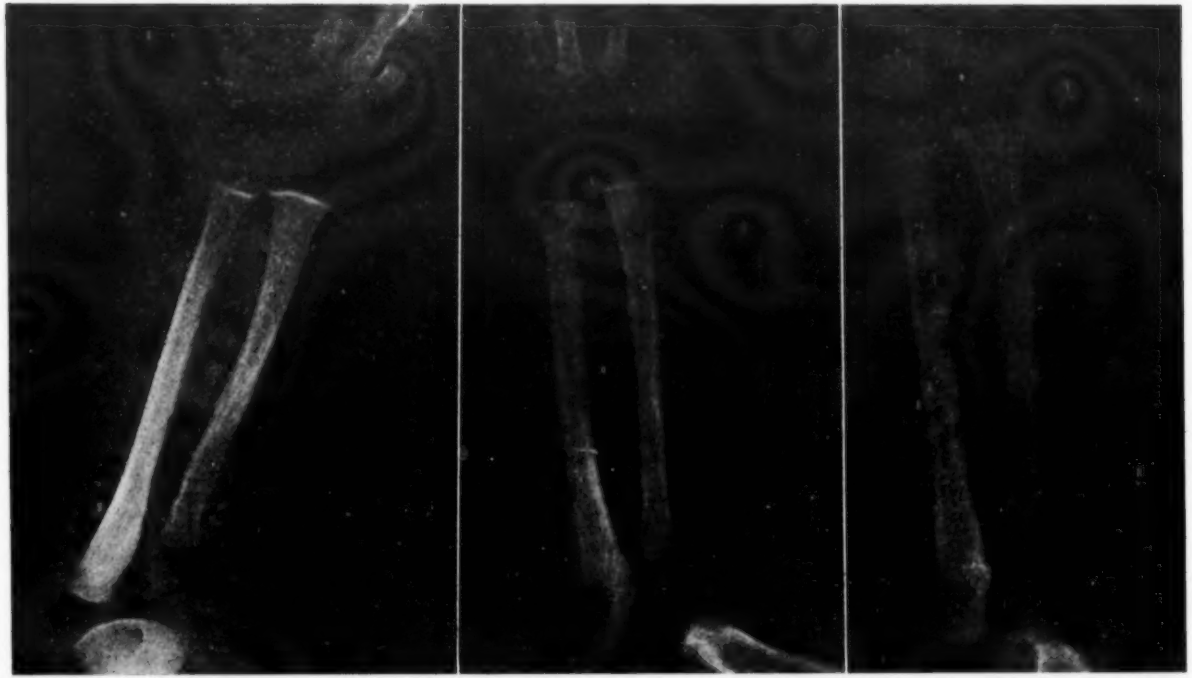
There was little to indicate an endocrine dysfunction at the end of five months of treatment and the bone growth during this period had proceeded at a rate greater than the average (Fig. 1 and Fig. 2*B, C*). Clinical improvement was uninterrupted for the next three months but bone measurements, instead of increasing more rapidly than average, now paralleled the mean curve. The intake of thyroid was increased in an effort to speed up calcification but no change was noted and the appearance of tachycardia and irritability led to resumption of the earlier dose; suggesting, in this case at least, that the amount of medication necessary to provide normal bone increase is also the optimum for other requirements. The remainder of her course was uneventful and at 2 years of age she was within average range for size and behavior.

The second patient (Case 2, No. 123916) was also 4½ months old when seen by us and his story was generally similar to that of the first case. He was physically a fully manifest cretin while absence of the carpal centers, abnormally short radii, and dense epiphyseal plates were observed by x-ray. Treatment with 45 mg. of desiccated thyroid (Armour) daily brought about dramatic clinical improvement and resumption of bone growth. After six weeks of treatment the dose was reduced to 30 mg. daily because of irritability, and this resulted in a slight regression for the rate of calcification during the next two months (Fig. 1). He was returned to the original amount but during the next two and one-half months received only hit-and-miss therapy. While there was little to suggest inadequate treatment clinically, he had made practically no increase in long bone growth.

We did not see this child again for over seven months and then, when brought back by a health officer, he was to all intents an untreated cretin. He had received practically no thyroid and all of the original stigmata were in full bloom. Supervised care was arranged and 60 mg. of thyroid given daily. Clinical and roentgenoscopic response was immediate and by 2 years of age he had recovered much of the lost ground.

A subsequent pregnancy by the mother of this infant also terminated with the birth of a cretin. The mother was seen by a competent endocrinologist and no defect in her own metabolism was found. The new baby was brought

*This has been, in our experience, the usual sequence of events. The athyreotic fetus of a normal mother is undoubtedly protected to a variable extent by the transplacental passage of hormone. Frank symptoms of deficiency are consequently not present at birth but develop gradually thereafter and at a rate destinctive to the individual. This rate often seems to be influenced by the amount and duration of breast feeding but whether through secretion of thyroid substances in the milk or through better nutrition is open to question.



A. *B.* *C.*

Fig. 2.—Roentgenograms of Case 1. *A*, Film before treatment (4½ months of age). *B*, Four weeks later; a zone of normal bone has appeared distal to the dense scar. *C*, After four months of therapy; the carpal centers are appearing and the remnants of the old scar are still visible.

Fig. 3.—Roentgenograms of Case 3. *A*, Film before treatment. *B*, After four weeks of therapy showing a good margin of normal bone. *C*, After two months of therapy the scar can still be discerned. *D*, Films at 8 months of age, five months since beginning treatment. Carpal centers have not appeared, but bone growth is progressing at an average rate.

under care by 3 months and his course is not recorded in detail since it paralleled closely the events in Case 3.

The third patient (Case 3, No. 132388) interested us especially since we had followed him since birth. He had been a big baby, weighing over 9 pounds, and he had passed an uneventful first month. A note was made at the end of the second month to watch him closely since his behavior was not up to expectancy. By the third month he showed considerable evidence of myxedema and films revealed a dense epiphyseal plate and absence of the carpal bones (Fig. 3*A*). The radii were not abnormally short; a finding easily explained by reference to Fig. 1, where it will be seen that an infant with radii well above the mean at birth might still remain within normal limits for the three months' standard, even if no growth had taken place.

Administration of desiccated thyroid (Armour), 45 mg. daily, brought about immediate return to normal progress. His radii increased at first more rapidly than average, then began to parallel closely the mean (Fig. 1 and Fig. 3*B, C, D*).

These cases can be summarized briefly. The first patient was treated at 4½ months of age after her deficiency was well established. Her progress was steadily upward and serial observations of her radii paralleled closely the clinical improvement. The second infant was received at the same stage of his disease as was the first. His treatment, however, was sporadic and inadequate during a good portion of the period of observation. Clinical improvement was never constant and the curve of his bone growth provided a most accurate record of his course. The third child was started on treatment before evidence of deficiency was fully manifest and his progress has been in every way comparable to that of a normal child. Films of his radii have reflected this course accurately and provide a clear baseline for further regulation of his regime.

DISCUSSION

We would stress two features with regard to the value of serial roentgenograms of long bones in congenital myxedema. First, a hard, densely calcified epiphyseal plate is as dependable a finding as is retardation in the appearance of ossification centers. This typical epiphyseal plate is present by the time suspicions are aroused on clinical grounds. It does not resemble the plate seen in rickets, scurvy, syphilis, or lead poisoning and has not been encountered by us in films other than those of myxedematous patients. Second, the administration of thyroid substance results in an almost immediate resumption of growth and replacement of the abnormal line by newly calcified bone. Adequate treatment causes calcification first at a rate greater than average for normal infants, later growth which parallels this normal curve. Reduction of thyroid intake is reflected by decreased bone growth and this decrease can be measured radiographically before outstanding clinical signs of deficiency appear.

These observations can easily be applied to problems involving differentiation of thyroid deficiency from other states characterized by retardation in growth and development. The administration of a therapeutic test with thyroid substance should be reflected visibly in the long bones within three to four weeks, if a true lack is present, and, if not, no changes will be observed. We recently saw an infant of 6 months who had been treated with thyroid substance as a cretin. It was our belief that the true diagnosis was mongolian

idiocy. Films showed fairly normal carpal bones, a normal epiphyseal plate, and radial measurements at the mean. The contention was that these findings were due to the therapy, but a test was easily arranged; thyroid was omitted for four weeks and during this period the bone growth continued to parallel the normal curve—such data were perfectly acceptable to the physician and the family.

No attempt has been made to extend this standard beyond 2 years of age since bone growth is considerably slower thereafter and since other norms for thyroid function are easily applicable to older children.

CONCLUSIONS

1. Characteristic changes in the long bones of cretins are of diagnostic value and also serve as guides to the regulation of treatment.
2. A curve expressing the growth of the radius in infants without evidence of thyroid deficiency is presented.
3. Several cases are accounted to illustrate the use of long bone studies.

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS WITH SEVEN-YEAR RECOVERY—CASE REPORT

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ACUTE disseminated lupus erythematosus is regarded as a uniformly fatal disease. The less fulminating varieties sometimes undergo spontaneous remission, but recurrences are the rule, and death occurs in a relapse usually within one year. The present report deals with a case which is an exception to these observations; it concerns a boy who suffered the most acute and severe form of the disease, who was apparently moribund for days, and yet survived. He not only made a complete recovery, but in a seven-year follow-up period has had no recurrence and has enjoyed robust health.

CASE REPORT

M. G., a 14-year-old schoolboy, was admitted to the Pediatric Service of the New Haven Hospital on Feb. 23, 1938, complaining of an erythematous eruption on the face, of two months' duration. His past and family histories were not remarkable. The parents and three sisters were living and well; there were no familial diseases and no tendencies toward allergic manifestations. The boy had had pertussis, measles, and mumps, but had never had scarlet fever, rheumatic fever, or nephritis.

The present illness began two months before entry with the appearance of a vesicular rash on the ears. The bases of the lesions and the surrounding skin were erythematous and slightly pruritic. Within a few days the vesicles broke down and the lesions became scaly. The erythema and scaly maculopapular lesions spread gradually over both cheeks and became confluent; two weeks before admission they appeared on the extremities, chest, back, and trunk. During the spread of the facial lesions, there was considerable edema of the face and eyelids, but this had subsided with entry. Aside from malaise and chilly sensations for the week before admission, there were no striking systemic manifestations.

I am indebted to Dr. Grover F. Powers of the Pediatric Department, Yale University School of Medicine for assistance in preparing this report.

From the Section of Preventive Medicine, Yale University School of Medicine, and the Children's Clinic, New Haven Hospital.

There was no known fever, and no joint pains. For a few days before admission there was considerable oozing of blood from the nares and from the oral mucous membranes.

Physical Examination.—Temperature, 30° C.; *pulse,* 88; *respiration,* 22; *blood pressure,* 115/70.

The child was a pale, somewhat underdeveloped and undernourished Italian boy, appearing chronically ill. *Skin:* There were raised, roughened, erythematous areas with dry, thin scaling on their surfaces symmetrically distributed over the ears, cheeks, and nose; many of the larger lesions were confluent; the margins were definite and irregular (Fig. 1). Similar but more circumscribed lesions (1 to 4 mm. to 1 cm. in size) were present over the chest, back, arms, and legs. The dorsal and palmar surfaces of both hands were covered with erythematous macules (Figs. 2, 3).

Fig. 1.—Appearance of facial lesions early in the patient's hospital course.

Lymph Nodes: Moderate generalized enlargement, most marked in the cervical and inguinal chains; nodes firm and nontender. *Head:* Thick black hair; scalp clear. *Eyes, ears:* No abnormalities. *Nose:* Mucosa covered with dry, caked blood. *Mouth:* Mucosa reddened and hemorrhagic in spots; tongue coated; teeth carious. *Throat:* Slight postnasal discharge. *Lungs:* Clear. *Heart:* Point of maximal impulse in the fifth intercostal space, just outside the midclavicular line. Soft systolic murmur audible at the apex and base. Sounds of good quality. P_2 reduplicated. *Abdomen:* Liver edge felt 2 fingerbreadths below the right costal margin. Spleen, 1 fingerbreadth below the left costal margin, firm in consistency. *Genitalia:* Normal male. *Extremities:* Normal-appearing except for the skin lesions already noted. *Reflexes:* Physiological.

Fig. 2.—Palmar lesions.

Fig. 3.—Lesions on the dorsum of the hands.

Admission Laboratory Data.—Blood: Red blood cells, 3,280,000; hemoglobin, 9.5 Gm.; white blood cells, 4,700; P 74 (segmented, 60; nonsegmented, 14); leucocytes, 23; monocytes, 3; platelets, 360,000. Red blood cells fragility normal. Corrected sedimentation rate, 26. *Urine:* Acid; specific gravity, 1.028; albumin, 1 plus; sugar, negative; sediment: occasional casts, rare white blood cells. *Tuberculin:* Negative 1/50. *Schick:* Negative. *Kahn:* Negative. *Nose, throat,* and *blood cultures:* Negative. *Fibrinolysin:* No lysis in twenty-four hours. *Nonprotein nitrogen:* 34 mg. per cent. *Serum proteins:* 6.7 Gm. (albumin, 3.5; globulin, 3.2). *Electrocardiogram:* Normal except for sinus tachycardia. *Chest x-ray* (portable): Normal cardiac silhouette; film unsatisfactory for lung fields.

Course.—In the two weeks following admission, the patient grew steadily worse (Fig. 4). The erythematous lesions continued to spread over the extremities, finger tips, and back. The temperature ranged between 39 and 40° C., and at one time reached 41° C. There were mental confusion and disorientation. Therapeutic measures at this time included transfusions, parenteral fluids, liver extract, and pentnucleotide, none being attended by any improvement.

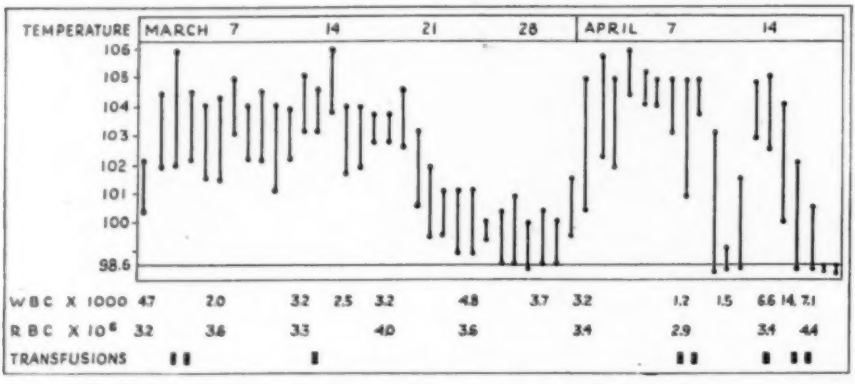

Fig. 4.—The hospital course (March to April, 1938).

On the fifteenth hospital day, the child's condition was grave. Respirations were rapid and labored, and fine moist râles were heard over both lung fields. No change in the heart signs were noted, but x-ray of the chest revealed marked enlargement of the cardiac shadow, and basal congestion of the lung fields (Fig. 5). The spleen remained slightly enlarged, but the liver increased in size and was felt 4 fingerbreadths below the costal margin. Digitalis was begun at this time. An electrocardiogram taken one hour after the patient had received 0.2 Gm. by mouth showed extremely low voltage and slight inversion of the T waves in Leads I and II.

During the next few days the patient continued to be irrational and gradually developed a stiff neck. Lumbar puncture, however, revealed normal dynamics and normal cerebrospinal fluid. A severe nonproductive cough developed and a loud friction rub was heard over the left upper lobe of the lung. On the twentieth hospital day, the temperature dropped to normal for the first time, and there was marked improvement in the general condition. The response to digitalis was excellent; the cardiac size diminished; the heart sounds improved in quality, and no murmurs were heard. The pleural friction rub persisted for some days but gradually cleared. The liver and spleen remained enlarged. The skin lesions gradually faded from bright red to a more dusky hue, and a fine brawny desquamation occurred over the involved areas.

After ten days of continued improvement, there was a sudden relapse with a rise in temperature to 40°, a fiery exacerbation of all the skin and oral mucous membrane lesions, with considerable gingival bleeding. Cardiac enlargement was again noted, as well as a systolic apical murmur and gallop rhythm. Râles and a friction rub were heard at the left lung base; the liver and spleen remained large, and the abdomen distended. A deep decubitus ulcer appeared over the sacrum. The child was lethargic and often irrational. The laboratory findings were similar to the previous ones, except that the leucopenia was even more marked (lowest, 1,250, with 67 per cent lymphocytes) and the hemoglobin

dropped rapidly to 7.5 Gm. A blood culture was sterile. The urine was negative except for a 1 to 2 plus albumin, and 0 to 2 red blood cells per high power field on one occasion. Treatment at this time consisted of repeated transfusions, parenteral liver extract, and nicotinic acid, 500 mg. daily.

On the eighth day of the exacerbation, a firm swelling was noted over the right mandibular area, which rapidly involved the submaxillary area and the upper neck. A diffuse cellulitis of the floor of the mouth appeared at the same time. A diagnosis of Ludwig's angina was made; the septic course continued, and four days later, incision and drainage was deemed advisable. This was carried out under local anesthetic, but no pus was encountered. The wound was packed open. The immediate postoperative condition was precarious, but within a few days improvement began: the temperature fell, the cellulitis subsided, and the general condition was much better. At this time, the white blood cell count began to rise, first to 6,000 and thence to 14,000 in the course of the succeeding weeks. A small fluctuant area appeared in the wound near the site of the first incision five days postoperatively. This was opened and one ounce of green pus was obtained. Culture of this material grew hemolytic *staphylococcus aureus* and *albus*, alpha and gamma streptococci.

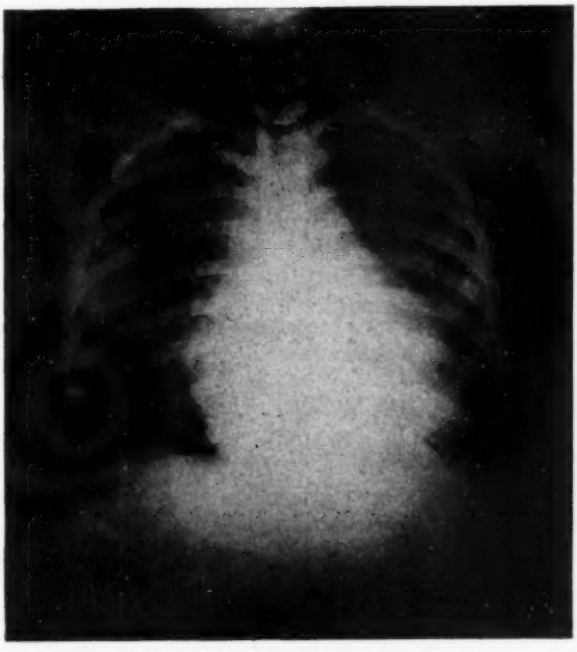

Fig. 5.—A portable film made on March 15, 1938.

The subsequent course was one of steady improvement. The neck wound healed without difficulty; the temperature remained normal; the skin lesions healed, leaving brown pigmentation; there was continued weight gain and increase in general well-being. During convalescence there was a complete loss of scalp hair, associated with scaling and desquamation of the scalp.

The patient was discharged three months and two days after entry, with the diagnosis of acute disseminated lupus erythematosus, in remission. He was seen in the outpatient department at intervals during the next ten months, at the end of which time his recovery appeared to be almost complete. There was still a patch of light pigmentation and atrophy of the skin over the nose and cheeks but no activity of the disease. Further follow-up seven years later revealed that the patient, who was then out of the State, had been in excellent health since discharge from the clinic. He had passed his physical examination for the Army, and according to last reports (January, 1945) was on active duty in the Pacific area.

COMMENT

There have been numerous cases of acute disseminated lupus erythematosus reported in the literature, almost all of them fatal within a period of weeks or months, sometimes within several years. O'Leary[1] studied forty-seven patients with disseminated lupus, twenty of whom had the acute form of the disease. All of these patients died—the average time interval from the onset of symptoms to death being nine months. Of 27 patients in the same series with the subacute form of the disease, eight died and seven were apparently cured; the eight fatalities occurred on an average of four and one-half years after the dissemination of the disease. Mook and his associates[2] reported thirteen cases of acute disseminated lupus erythematosus, of which nine patients died and four disappeared. Six of the nine deaths occurred within one year (two to twelve months) and three lived two and one-half, three, and six years, after onset. Six of nine cases reported by Madden[3] were fatal within a period of from twelve days to ten months. Reifenstein and his associates[4] tabulated the duration of the disease in eighteen fatal cases (seventeen collected from the literature) and found it to be under one year in nine, one to two years in three, two to three years in one, and three to four years in three.

Innumerable therapeutic measures have been tried, but in the final evaluation of each of these, no benefit was observed consistently with any one, except in a general supportive way. There has been one report[5] of striking improvement following the administration of "Detoxin," a high molecular protein compound rich in sulfur. In the past five years, the sulfonamides have been used[6-8] with variable results. In about one-half of the cases, improvement and even "cures" have been observed, while in the other half, no change was noted one way or another. In the cases reported as cured, the follow-ups have been brief, none longer than two years, and most of these patients have been only moderately sick at the height of their disease.

The course of the patient herein reported is unusual in that remission occurred in spite of the extreme severity of the disease: the patient had widespread visceral involvement, and was apparently moribund for days. His survival was unexpected, and his return to complete health for seven years is without parallel in the literature. Such a spontaneous recovery serves to emphasize the danger of attributing favorable results to sulfonamides and other drugs in a disease of unknown etiology which is prone to unpredictable remissions.

SUMMARY

A case of acute disseminated lupus erythematosus with severe skin and visceral involvement and a septic complication is reported. Spontaneous resolution of the disease occurred, and the patient is healthy and vigorous after seven years.

REFERENCES

1. O'Leary, P. A.: Minnesota Med. 17: 637, 1934.
2. Mook, W. H., Weiss, R. S., and Bromberg, L. K.: Arch. Dermat. & Syph. 24: 786, 1931.
3. Madden, J. F.: Arch. Dermat. & Syph. 25: 854, 1932.
4. Reifenstein, E. C., Reifenstein, E. C., Jr., and Reifenstein, G. H.: Arch. Int. Med. 63: 553, 1939.
5. Ervenich, Paul: Med. Klin. 33: 233, 1937.
6. Wile, W. J., and Holman, H. H.: Arch. Dermat. & Syph. 42: 1059, 1940.
7. Hopkins, H. H.: Arch. Dermat. & Syph. 43: 833, 1941.
8. Pearson, J. E. G.: Brit. M. J. 1: 253, 1943.

EDEMA WITH HYPOPROTEINEMIA DUE TO A CONGENITAL DEFECT IN PROTEIN FORMATION

(Case Report)

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FOLLOWING studies of edema in starvation and in nephrosis, the relationship between edema and hypoproteinemia has become well known. Hypoproteinemia and the resulting edema are explained by "lack or loss" of protein in the body. The prototype of the former (lack) is found in starvation with hunger edema and that of the latter (loss) in nephrosis, where protein is lost in the urine.

Within recent years an occasional case has been described, where edema and hypoproteinemia were present without starvation or nephrotic albuminuria. These cases with one exception (Thompson, McQuarrie, and Bell[13]) were observed in adults.

An unusual case of this kind in a child came under our observation and is here reported.

Patient D. E. has been known to the senior author since the age of 12 weeks. It was only after eleven years that the parents were finally persuaded to consent to hospitalization of the child so that careful studies could be carried out.

There was a history of edema of the mother as a young adult. This occurred in Europe during World War I, during a period of protein starvation. The mother's serum-albumin at the time of child's hospitalization was 5.5 Gm. per cent, globulin 1.1 Gm. per cent. The father's serum-albumin was 4.1 Gm. per cent and the globulin 1.9 Gm. per cent.

The prenatal period and delivery of the patient were normal. A hematoma of the sternocleidomastoid muscle and edema of the genital region complicated the neonatal period. At 12 weeks of age, swelling of the neck and groin appeared. This persisted through the first year. Recurrent distention of the abdomen by fluid and swelling of the lower extremities reappeared at 5 years of age. These symptoms diminished on bed rest, returning when the child was up and about. There were occasional bouts of urticaria. Dependent edema was prominent from the age of 8. The intensity of the edema varied, at times becoming extreme particularly in the legs. Ascites was also marked. The edema in the face was usually less marked although the eyelids and the face resembled that seen in a typical case of nephrosis or nephritis. The urine frequently examined was always free from albumen or formed elements. High protein diet and thyreoid were without effect.

There was no susceptibility to infection of the nose or throat and other parts of the respiratory tract. The child had mumps at the age of 7 and measles at 10.

The diet was mixed, adequate, and the general state of nutrition had always been good.

Physical examination revealed a well-developed and well-nourished 11-year-old female child, who appeared neither acutely nor chronically ill. There was some puffiness of the eyelids and a brawny pitting edema of the lower extremities. The edema was moderate in amount, not massive. There was a soft precordial systolic murmur. A small amount of fluid appeared to be present in the abdomen. The ocular fundi and the capillaries of the fingers showed venous congestion; otherwise the examination was negative.

On bed rest, the edema subsided, and the patient's weight dropped from 92 to 85 pounds with the loss of fluid. The edema recurred when the patient walked about. A high protein, high vitamin diet, as well as oral amino acid therapy, had no effect whatsoever.

The basic defect in the patient was mirrored in the serum proteins. The serum-albumin, by the Kjeldahl method was 3.3 Gm. per cent, and the globulin was 0.8 Gm. per cent. Electrophoretic analysis revealed practically no migration of protein in the gamma globulin fraction.

From the Pediatric Department of Mount Sinai Hospital (Dr. Murray Bass).
†Killed in action in the Pacific Area.

Laboratory studies included the following:

The basal metabolic rate was minus 11 per cent.

X-rays of the long bones were normal. X-rays of the small and large intestines were normal, including motility. X-ray of the chest revealed a small calcified focus over the second rib. The Mantoux test, however, was negative. The electrocardiogram was normal. The phonocardiogram revealed an apical and pulmonic systolic murmur, with P_2 reduplicated and a physiologic third heart sound at the apex. Venous pressure was 9.5 cm. of water. The circulation time was five seconds by the ether method, fourteen seconds by the saccharin method, normal circulatory rates. The blood pressure ranged about 110/40. Gastric analysis revealed free hydrochloric acid with a normal total acidity. Urine was normal. Concentration was effective to 1.032. Urine urea was 600 mg. per cent. Blood urea 11.0 mg. per cent. The urea clearance test showed normal function. The McClure-Aldrich intradermal saline test for edema showed disappearance of the nodule in thirty minutes, a positive reaction.

Scratch tests with food, inhalant, and pollen antigens were negative.

Hematological study revealed a normal blood smear; hemoglobin, 100 per cent; red blood count, 5.0 million; white blood count, 8,000 with a normal differential including 1.0 per cent eosinophiles; no reticulocytes; platelets 200,000 per 1 mm.;^{3} hematocrit 41 per cent; fragility test: hemolysis began at .44 and was complete from 0.32 down. Coagulation time, five minutes; bleeding time, three minutes. The specific gravity of the blood was 1.0234 (normal 1.0225 to 1.0335); there was a normal red cell volume of 81 mm.,^{3} and a normal red cell diameter of 7.0 μ; there was a low blood viscosity of 1.359 (normal 1.734).

Blood chemistry studies did not give any definite evidence of liver or renal damage. The blood Wassermann test was negative; the blood chlorides were 655 mg. per cent; the carbon dioxide combining power was 63 per cent; the calcium was 8.3 mg. per cent; phosphorus, 4.3 per cent, a very slight deviation from the normal; phosphatase was 27 King Armstrong units, suggestive of liver damage; the blood cholesterol was 300 mg. per cent and the esters were 225 mg. per cent; cephalin flocculation test positive in hepatitis was negative; the hippuric acid liver test showed borderline figures, 1 Gm. of hippuric acid was excreted after ingestion of 2½ Gm. of benzoic acid. Galactose tolerance test was normal. Glucose tolerance test showed a flat curve, starting at 70 mg. per cent rising to 100 and going down to 65 mg. per cent. Fibrinogen was 330 mg. per cent. Amino acids were 7.7 mg. per cent; prothrombin test was normal.

Urine studies relative to the phenols as an index of amino acid metabolism revealed a value of 12.7 for the volatile phenols (normal 15 to 20); a value of 97.5 for reduced phenols (normal 100 to 160); aromatic hydroxyphenols 16.9 (normal 30 to 35). The low values for aromatic hydroxyphenols suggest a defect in amino acid metabolism but sufficient standardization has not been done to warrant final conclusions. Xanthoprotein reaction of urine, 19 (normal twenty-five to thirty).

DISCUSSION

Trevarrow and associates[3] in a study of plasma protein values from birth to adulthood, gives the normal for the patient's age as 4.7 plus or minus .32 Gm. per cent for albumin, and 2.0 plus or minus .34 Gm. per cent for globulin, and 6.94 plus or minus .47 Gm. per cent for total protein. Our patient showed a decrease in both albumin and globulin fractions with the greatest decrease in the latter fraction.

Calculation of the colloid osmotic pressure of the plasma can be made by the formula of Wells and associates;[4] P (colloid osmotic pressure in millimeters of water) equals T (total protein in grams) × (5.9 × albumin plus 21.4). The result obtained for this patient was 22.3 cm. of water. According to Weech,[5] the normal colloid osmotic pressure of plasma is 29 to 40 cm. of water, and the mechanical pressure of the capillaries 45 cm. at the arterial ends and 22 cm. at the venous end. The borderline state of edema shown clinically by the patient is in agreement with the figures. Considering critical values for protein of 2.5 to 4.0 Gm. for albumin and 5.5 Gm. for total protein[5] again indicates a borderline state of edema.

A large decrease in serum globulin is unusual. Kagan[6] studied 345 patients with hypoproteinemia and found the decrease due, almost invariably, to a decrease in albumin. He noted a low globulin only in premature infants, patients in early severe hemorrhage, and in advanced cirrhosis of the liver.

In an electrophoretic analysis of protein, fractions are differentiated by their rate of migration in solution through an electric field. In normal serum[7] such an analysis reveals 62.5 per cent albumin, 7.0 per cent alpha globulin, 13.2 per cent beta globulin, and 11.6 per cent gamma globulin. This patient had practically no migration in the gamma globulin fraction. The gamma globulin or similarly migrating fractions rises in cirrhosis of the liver, cardiac failure, during infections such as pneumonia and tuberculosis, and in response to immunization. In immunization the increase in the gamma globulin is quantitatively equal to the antibody rise.[8-11] The gamma globulin falls in nephrosis. The low globulin fraction in nephrosis is used as one of the explanations for the susceptibility to infection in that disease. Our patient had no clinical susceptibility to infection; on the contrary she was particularly free from the usual colds and sore throats. The presence of antibodies in the serum is shown by the negative Schick and Dick tests. The Mantoux test, however, was negative, despite a calcific focus noted in the x-ray of the chest. On attempts to stimulate antibody formation by the injection of diphtheria toxoid, typhoid vaccine, and pertussis vaccines she failed to develop a positive Widal, pertussis antibodies, or any rise in serum proteins.

The plasma proteins are found in the liver, reticulo-endothelial system, and bone marrow[6, 12] and in a case somewhat similar to ours reported by Thompson, McQuarrie, and Bell,[13] a possible hepatic origin is suggested. Their patient had a history of edema since the age of 13 months. The plasma albumin was 1.9 Gm. per cent and the globulin, 1.5 Gm. per cent. Diet did not affect the protein levels. Transfusion produced a remission which lasted a few weeks. There was no evidence of excessive destruction of protein. Although the edema began after a respiratory infection, it subsided coincidentally with an attack of pertussis. After surviving one episode of pneumonia, the patient succumbed to a combined ear and lung infection. At autopsy, an atrophy of the hepatic cords, especially in the intermediate and peripheral zones of the lobules, was seen. There were neither fibrosis nor inflammatory signs present. The authors assumed the existence of a congenital anomaly in the function of the liver, due to a reduced amount of liver tissue.

Myers and Taylor[14] reported a 51-year-old male alcoholic who had edema since childhood. His serum albumin was 2.4 Gm. per cent, and his serum globulin was 1.2 Gm. per cent. Nitrogen balance studies revealed an ability to absorb protein and break down amino acids. Increased dietary protein did not change the nitrogen of the stools but increased the ammonia nitrogen of the urine. An achlorhydria was present.

One case of idiopathic hypoproteinemia is reported by Jungmann[15] with a total protein between 3.9 and 5.0 Gm. per cent. Three cases are reported by Meyer-Bisch.[16] All four had an achlorhydria.

Cope and Goadby[17] reported an adult with a six months' history of edema, whose albumin was 2.9 Gm. per cent; and globulin, 1.6 Gm. per cent, unaffected by diet.

Johanssen[18] reported a 25-year-old female with hypoproteinemia at whose autopsy hepatitis was found.

Binger and Keith[19] reported three cases of hypoproteinemia, all adults, with three to five years' history of edema. One case, a male aged 62 years, had a serum albumin of 2.6 Gm. per cent and a serum globulin of 1.4 Gm. per cent, and showed at autopsy mild interstitial hepatitis and some atrophy of the pancreatic acini and islands.

Rytand[20] reported a 24-year-old female with an eight-year history of edema. The serum albumin was 2.3 Gm. per cent, and the globulin was 1.3 Gm. per cent. High protein diet, amino acids, and vitamin B therapy were of no avail. The electrophoretic pattern was normal. There was a slight eosinophilia, and a slight increase in thickness of the red cells.

The patient we have reported here probably has some congenital deficiency in the liver, bone marrow, or reticulo-endothelial system which accounts for her inability to properly synthesize plasma proteins. The most probable site of pathology is the liver. It may be expected that with the further development of the child during puberty, the function of the liver will also improve with its growth. Thus the defect in the synthesis of the plasma protein may become less marked and even normal.

SUMMARY

A case of congenital hypoproteinemia is reported. There appeared to be a defective formation of albumin and globulin, particularly the gamma globulin. There was no susceptibility to infection although some deficiency in the formation of antibodies was noted. As the gamma globulin is accepted to be the main carrier of humoral antibodies it is surprising that the child enjoyed excellent health with no susceptibility to colds or other frequent childhood infections. The only disturbance has been the edema. The child was never absent from school on account of tonsillitis or colds. This suggests the possibility that humoral immunity may not be the only basis for an individual's resistance against infection but that other mechanisms, particularly the cellular immunity, may play a definite role in producing antibodies rapidly. The negative Schick and Dick tests demonstrate the presence of a certain amount of humoral antibodies.

A high protein diet, amino acids orally, and antigenic stimulation did not affect the level of the serum protein nor the clinical picture of recurrent edema. There was a suggestion of liver damage in the laboratory studies. There was no change in the clinical picture of recurrent edema during the period of observation from birth to the age of 12 years.

The fact that edema may be caused by a disturbance of the liver function suggests that the edema in nephrosis and even other symptoms of nephrosis may be due to liver damage. Whereas the symptoms in our case may have their basis in an insufficient production of normal protein, particularly of gamma globulin, the symptoms of nephrosis may be due not only to the reduction in the manufacture of normal proteins, but also to the production of abnormal protein. In this connection it is interesting to note that according to investigations of Goettsch and Reeves[21] the albumin fraction of plasma in nephrosis is immunologically different from normal protein. Whether normal or abnormal proteins are formed seems to be more important in the pathogenesis of nephrosis and of other forms of edema than the simple loss of protein by the kidney or the lack of sufficient amount of protein in the diet.

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REFERENCES

1. Melnick, D., Cowgill, G. R.: Yale J. Biol. & Med. 10: 49, 1937.
2. Levin, L., Leathem, J. H.: Am. J. Physiol. 136: 306, 1942.
3. Trevarrow, V., Kaser, M., Patterson, J. P., Hill, R. M.: J. Lab. & Clin. Med. 27: 417, 1942.
4. Wells, H. S., Youmans, John B., and Miller, D. G.: J. Clin. Investigation 12: 1103, 1933.
5. Weech, A. A.: Internat. Clin. 2: 223, 1936.
6. Kagan, B. M.: Arch. Int. Med. 71: 157, 1943.
7. Leutcher, J. H.: J. Clin. Investigation 20: 99, 1941.
8. Bjornboe, M.: J. Immunol. 37: 201, 1939.
9. Longsworth, L. G., Shedlovsky, T., MacInnes, D. A.: J. Exper. Med. 70: 399, 1939.
10. Marrack, J. H.: The Chemistry of Antigens and Antibodies, Great Britain Medical Research Council, Special Report Series, No. 230, 1938.
11. Tiselius, A., and Kabat, E.: Science 87: 416, 1938.
12. Madden, Sidney C., and Whipple, George H.: Physiol. Rev. 20: 200, 1940.
13. Thompson, W. H., McQuarrie, I., and Bell, E. T.: J. Pediat. 9: 604, 1936.
14. Myers, W. K., and Taylor, H. F. L.: J. A. M. A. 101: 198, 1933.
15. Jungmann, Paul: Klin. Wchnschr. 1: 1546, 1922.
16. Meyer-Bisch, R.: Klin. Wchnschr. 4: 588, 1925.
17. Cope, C., L., and Goadby, H. K.: Lancet 1: 1038, 1935.
18. Johanssen, A. H.: Acta path. et microbiol. Scandinav, Supp. 37, p. 272, 1938.
19. Binger, M. W., and Keith, N. M.: J. A. M. A. 1: 109, 1937.
20. Rytand, David A.: Arch. Int. Med. 251: 69, 1942.
21. Goettsch, E., and Reeves, E. B.: J. Clin. Investigation 15: 173, 1936.
22. Bloomfield, A. L.: J. Exper. Med. 57: 705, 1933.

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COMPARATIVE STUDY AND SIGNIFICANCE OF THE TUBERCULIN PATCH AND MANTOUX TESTS IN CHILDREN

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THE following is a report of observations extending over a period from May, 1938, to October, 1944, making a comparative study of the results of the Mantoux and patch tuberculin skin tests applied to children of both sexes about equally distributed, from 8 months to 14 years of age in an orphan asylum, three kindergarten nurseries, and from private practice. In all, there were 1,074 children. Of these, 112 children received the patch tuberculin test only, and 962 children received both the Mantoux and patch tests. The results of the reactions are presented in Tables I and II.

In 250 of the children tested (Vollmer) tuberculin patch tests were used.* The 824 remaining children were tested with patch test material made up as follows: one-inch wide adhesive tape was cut into three-inch strips, upon which were placed three small one-half inch rectangular patches of white filter paper one-half inch apart and equidistant from the top and bottom. The center square was used for a control having no tuberculin on it, whereas the two end squares were impregnated with undiluted old tuberculin.† The selective sites for applying the patch tests were the small of the back between the scapulae in young children and the biceps region in older children. The skin was first swabbed with acetone to remove fatty material and then dried. The tuberculin adhesive strip was applied snugly to the skin to assure a close contact between it and the

*Vollmer patch test material was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

†Mantoux and old tuberculin test material was supplied by the Bureau of Laboratories, Department of Health, New York, N. Y.

TABLE I. CHILDREN WHO RECEIVED THE PATCH TUBERCULIN TEST ONLY

AGE	CHILDREN TESTED (NO.)	REACTIONS	
		POSITIVE	NEGATIVE
1 to 14 yr.	112	13 (11.5%)	99 (88.5%)

TABLE II. CHILDREN WHO RECEIVED BOTH TESTS, PATCH AND MANTOUX TUBERCULIN

AGE	CHILDREN TESTED (NO.)	TUBERCULIN REACTIONS		POSITIVE REACTIONS		
		POSITIVE	NEGATIVE	TO PATCH AND MANTOUX TESTS	TO PATCH TEST ONLY	TO MANTOUX TEST ONLY
8 mo. to 14 yr.	962	104 (10.8%)	858 (89.2%)	96 (92.3%*)	3 (2,9%)	5 (4.8%)

*Of the positive cases.

tuberculin. The mother or nurse in charge was instructed to leave the patch on, undisturbed and dry, for two days, after which time the adhesive strip was removed and the area inspected. Any complaint by the child of feeling intense itching, or a burning sensation, or pain at the site of the patch after its application was to be reported. Readings of the reaction were recorded two days later or on the fourth day after applying the patch to the skin. The Mantoux intradermal tuberculin tests were administered on the anterior surface of the right forearm of each child. Inspections for recording the mantoux tuberculin reactions were made the following day and after forty-eight and seventy-two hours, respectively. During 1940 the time interval between the patch and Mantoux tests for each child was spaced one month apart. This was done to observe comparative differences of reactivity and for focal reactions (reported often by clinicians). During this period, no focal reactions or constitutional symptoms resulted from either of the tests performed. From then on the two tests were applied at the same time at their respective sites. Faulty technic may account for focal reactions or constitutional symptoms from the Mantoux intradermal injections.

TABLE III. CHILDREN WHO RECEIVED BOTH TESTS, MANTOUX AND PATCH TUBERCULIN, DIVIDED INTO THREE AGE GROUPS

AGE GROUPS	CHILDREN TESTED (NO.)	TUBERCULIN REACTIONS		POSITIVE REACTIONS		
		NEGATIVE	POSITIVE	TO PATCH AND MANTOUX TESTS	TO MANTOUX TEST ONLY	TO PATCH TEST ONLY
8 mo. to 4 yr.	297	275 (92.5%)	22 (7.5%)	22 (100%)	0	0
4 to 10 yr.	414	369 (89.1%)	45 (10.9%)	40 (89%*)	3 (6.6%*)	2 (4.4%*)
10 to 14 yr.	251	214 (85%)	37 (15%)	34 (92%*)	2 (5.3%*)	1 (2.7%*)

*Of the positive cases.

In Table III is a summary of observations made among 962 children divided into three age groups in which the youngest group showed 7.5 per cent positive reactors as compared with 10.9 per cent of the middle age group and 15 per cent of the oldest age group. The youngest group also showed 100 per cent of positive reactors for both tests, the patch and Mantoux. The accuracy of both tests compare favorably considering that in the middle age group of children there were 89 per cent positive reactors and in the older children 92 per cent positive reactors to the patch and Mantoux tuberculin tests.

Laboratory and clinical follow-up work among the tuberculin positive children revealed normal and differential white cell counts except for a slight increase in monocytes in 12 per cent of them. The blood sedimentation tests

showed an increased sedimentation rate of from 15 per cent to 30 per cent, in 62 per cent of the children. X-ray films of the chest showed calcified areas in the tracheobronchial glands in 40 per cent, and in 63 per cent of the cases there were increased density shadows along the bronchial tree, more so at the hilus. In none of the children was there found acid fast bacilli in the sputum, gastric contents, or in smears taken from the oral pharyngeal area. There were no significant temperature elevations.

DISCUSSION

The tuberculin reaction is an immunity reaction and shows, when positive, that the bacillus at some time has entered, and the body has responded defensively. The tuberculin skin test may be the means of detecting a potential community focus of infectivity. While the tuberculin patch test is useful in any public health campaign to test the tuberculin reactivity of sections of the population, it is of particular use for testing infants and preschool age children. Finkelstein[1] found that the first cutaneous tuberculin tests in tubercular infants were frequently negative. A second or third tuberculin test may be necessary before the true condition can be revealed through a positive tuberculin reaction. A small per cent of patients who fail to react to either test, who may still be sensitive where infection is suspected, should be retested with higher concentrations of tuberculin by intradermal injection. Naegeli[2] and others found that most individuals past puberty have tuberculosis showing tuberculous lesions at necropsy. All statistics show that the lethality is extremely high during the first two years of life and that it decreases with advancing age in spite of the increase in the incidence of infection. In other words, the power to produce immunity is insufficient in most infants and young children, a condition that is analogous to adults of nontuberculous races and regions. It is often said, "the younger the child the more significant a positive tuberculin reaction becomes; the older the child the more significant a negative one." An intense positive reaction may signify that a focus has been active recently. It need not imply that the disease is severe or progressing, as it may be receding at the time the test is made. It is quite possible that the infection may be limited to a few insignificant lymph glands. The age of the child, a careful case history, and the clinical picture must be relied upon in the analysis of the significance of a positive tuberculin reaction. It is unwise to administer tuberculin tests to children during fever or active disease. Sauer[3] reported obtaining negative tuberculin reactions in children during measles (in 100 per cent), scarlet fever (in 84 per cent), and diphtheria (in 12 per cent). Negative tuberculin tests were reported also in acute tuberculous infection with severe constitutional symptoms such as in miliary tuberculosis, tuberculous meningitis, and in tuberculous children with lobar pneumonia, influenza, erysipelas, and typhoid fever.

According to Sulzberger and Wise,[4] patch testing dates back a half century, when Jodassohn discovered a patch reaction in a case of eczema following an injection of a mercurial compound from a piece of mercurial plaster on the skin. The phenomenon presented in this patient at the site of this plaster contrasted to the rest of the skin surface gave Jodassohn the idea that one could elicit skin reactions in the hypersensitive by the simple method of applying the substances to the surface of the skin with adhesive tape without scratch or injection. Since then, many research workers and clinicians developed improved methods of local injection and various skin and patch tests. In 1907, Pirquet,[5] described the cutaneous tuberculin test; in 1909, Moro[6] reported on the tuberculin ointment percutaneous test; in 1910, Mantoux[7] wrote on the intradermal

tuberculin test; in 1912, Hamburger[8] explained the value of the subcutaneous tuberculin test; in 1937, Vollmer[9] described the patch tuberculin test; and in 1943, Grozin[10] modified the latter reporting on the visible patch test. I may add a word of comment to the inadvisability of using the visible tuberculin patch test since it tempts one to lift the lids to observe early reactions, and, in doing so, one may interrupt the close contact so necessary between the tuberculin patches and the skin and thereby may bring about inaccurate readings of the tuberculin reactions. In this work, I found the patch test to be a likeable procedure among the young children. The results of this comparative study of the patch and Mantoux tuberculin tests reveal the patch test to be economical, practical, sensitive, comparatively accurate, and easy to apply. The child feels at ease because he does not fear or anticipate getting an injection.

SUMMARY

In an orphan asylum, three kindergarten nurseries, and in private practice patch tuberculin tests were performed during a period from May, 1938, to October, 1944, upon 1,074 children; of these, 962 children received also the Mantoux intradermal tuberculin test. Boys and girls from 8 months to 14 years of age were tested. They were all presumably normal children tested in the course of periodic health examinations. In 112 children between the ages of 1 and 14 years who received the tuberculin patch tests, 13 children (11.5 per cent) gave positive tuberculin reactions. Of 962 children from 8 months to 14 years of age who received the patch and Mantoux tests, 104 children (10.8 per cent) gave positive tuberculin reactions, out of whom 96 children (or 92.3 per cent) gave positive tuberculin reactions to both the patch and Mantoux tests.

I wish to thank the Lederle Laboratories, Inc., for supplying Vollmer patch tuberculin test material; the Bureau of Laboratories, Department of Health, City of New York, for supplying the Mantoux test material and old tuberculin used in preparing patch tests strips used in this work. I appreciate the help received from Miss Charlotte Rosenzweig, nurse at the Israel Orphan Asylum, and the assistance received from the supervisors and attendants at the Hebrew Infant Home and Kindergarten Nursery, the Hamilton House Kindergarten Nursery, and the Kindergarten Nursery of the Jewish Settlement House of the East Side.

REFERENCES

1. Finkelstein, H.: Lehrbuch der Sauglingskrankheiten, Berlin, 1921, p. 431.
2. Naegeli, O.: Virchows Arch. f. Path. Anat. 160: 426, 1900.
3. Sauer, L. W.: In Abt, I. A.: Pediatrics, Philadelphia, 1924, W. B. Saunders Company, vol. 5, p. 567.
4. Sulzberger, M. B., and Wise, Fred: Arch. Dermat. & Syph. 23: 519, 1931.
5. Pirquet, C.: Wien. klin. Wchnschr. 20: 1123, 1907.
6. Moro, E.: Beitr. z. Klin. d. Tuberk. 12: 207, 1909.
7. Mantoux, C.: Presse. méd. 2: 10, 1910.
8. Hamburger, F.: Die Tuberkulose der Kindersalters, Vienna (1912).
9. Vollmer, H., and Goldberger E.: Am. J. Dis. Child. 54: 1019, 1937.
10. Grozin, M.: Am. J. Dis. Child. 66: 126, 1943.

HEMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FETALIS)

Clinical Analysis of Fifty-five Cases, With Special Reference to Pathogenesis, Prognosis, and Therapy

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MUCH has been written about hemolytic disease of the newborn since the discovery of the Rh factor by Landsteiner and Wiener[1] in 1940 and its association with this syndrome by Levine and co-workers.[2] An excellent summary of the present status of the Rh factor was recently published by Potter.[3] The present clinical study of the cases of hemolytic disease of the newborn treated at the New York Hospital during the last six years was undertaken to throw light on the following questions: What is the role of isoimmunization in the production of the syndrome? To what extent do the symptoms vary and how are they interrelated? When and how much should the infants be transfused? Is it possible to overtransfuse? Has any additional therapy besides transfusion proved beneficial? What is the most frequent cause of death?

MATERIAL AND METHODS

Review of the records revealed fifty-five infants with this condition treated on the pediatric service between July, 1938, and June, 1944. The infants showed most or all of the characteristic clinical signs—jaundice, progressive anemia, hepatomegaly, splenomegaly, hemorrhage, edema, excessive numbers of nucleated red blood cells in the circulating blood, and the typical pattern of Rh-negative blood in the mother and Rh-positive blood in the father and baby. Some of the infants were born in the Lying-In Hospital; others were referred from other hospitals or private pediatrists. Only liveborn babies were included.

Early Rh determinations were done in the laboratory of Dr. Philip Levine; in the past year, by the Blood Bank of the New York Hospital. Post-mortem examinations were performed by the Pathology Department of the New York Hospital.

RESULTS

Age, Sex, and Race.—Most of the infants were admitted during the first few days of life. Forty-four were 1 week old or less, and only seven were over 2 weeks of age at the time of admission. Twenty-nine of the patients were boys; twenty-six, girls. All were white.

Family History.—In thirteen instances family history revealed previous infants with hemolytic disease, including two sets of siblings (Cases 2 and 41, Cases 21 and 47). In addition, there were five patients in the period before Rh determinations were made whose family histories showed two or more abortions, stillbirths, or babies dying of unknown cause in the neonatal period. The series included one of each of two sets of twins. One pair was single ovum twins, occurring as the first pregnancy. One infant was stillborn and showed erythroblastosis at autopsy; the other (Case 13) had severe hemolytic disease of the newborn and died on the third day. The second set of twins was born in another hospital, where both babies were noted to be deeply jaundiced and pale

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TABLE I. CASES OF HEMOLYTIC DISEASE OF THE NEWBORN WITH ESSENTIAL CLINICAL AND LABORATORY FINDINGS*

CASE†	FH	RH	AGE (DAYS)	WT. (GM.)	JAUNDICE	HEPATOMEGALY	SPLENOMEGALY	EDEMA	INITIAL HGB. (GM.)	NUCLEATED R.B.C./100 W.B.C.	TOTAL TRANSFUSION (C.C.)	RH-NEG. TRANSFUSIONS (C.C.)	OUTCOME (LENGTH OF HOSPITALIZATION)
1 B. T.	–		NB	4,380	–	+	++	++	14.6	86	405		Died 12th day
2 I. G.	+	+	7	3,660	+	+	+	–	8.0	0	780		Well—59 days
3 G. L.	–		NB	3,410	+	++	++	–	12.0	105	380		Well—35 days
4 R. F.	–		18	3,340	+	++	++	–	8.5	0	315		Well—28 days
5 G. S.	–		NB	4,120	–	+	–	–	20.0	211	75		Died in 12 hrs.
6 G. M.	?		1	4,060	++	–	++	+	16.5	35	280		Well—10 days
7 B. L.	–		5	3,900	++	+	+	+	13.0	8	120		Died 7th day
8 R. H.	–		2	term	++	–	–	–	–	–	–		Died 3rd day
9 B. I.	–		4	–	++	+	+	–	12.6	many	–		Died 5th day
10 B. R.	–		NB	2,780	++	–	–	+	16.0	466	210		Died 4th day
11 G. B.	–		1	2,460	–	–	–	–	17.5	210	50		Died 3rd day
12 M. S.	–		NB	2,680	–	++	++	+	18.0	38	100		Well—11 days
13 G. T.	+		NB	2,080	–	–	–	–	12.5	85	80		Died 3rd day
14 L. A.	?		6	3,400	+	–	–	–	4.0	2	555		Well—25 days
15 A. B.	–		5	3,930	+	++	+	–	7.5	0	375		Well—31 days
16 B. G.	+	+	NB	3,840	–	+	–	–	23.0	76	250		Died 30th day
17 N. H.	–	+	NB	4,120	+	+	–	–	12.5	20	315	240	Well—15 days
18 J. C.	+	+	1	3,400	?	–	–	–	16.5	13	395		Well—21 days
(2nd adm.)			27	3,540	–	++	++	–	4.0	3	850		Well—64 days
19 D. M.	+	+	9	2,440	+	++	++	–	3.5	180	140		Well—43 days
20 B. B.	–		NB	2,110	+	–	–	–	9.0	19	110		Died 4th day
21 J. F.	+	+	NB	4,320	?	+	–	?	16.0	214	445		Well—44 days
22 G. I.	–		2	3,040	+	+	–	–	12.0	30	350		Well—29 days
23 B. B.	–	0	1	3,120	+	+	+	–	10.4	13	480		Well—40 days
24 B. F.	–		NB	2,480	+	+	–	+	18.0	32	50	50	Well—9 days
25 J. B.	–	+	NB	3,660	++	–	+	–	12.0	54	925		Well—64 days
26 G. W.	+	+	NB	3,300	++	+	+	+	17.5	15	521		Well—62 days
27 B. C.	–		1	4,020	–	–	+	–	14.5	7	100		Died 4th day
28 C. W.	–		NB	2,680	+	+	–	–	17.0	131	40		Well—12 days
29 S. S.	–	0	3	2,700	+	–	–	–	9.1	78	150	120	Well—18 days
30 B. E.	–		NB	2,700	+	+	+	–	13.0	88	–		Died in 4 hrs.
31 B. B.	–	+	8	3,200	–	++	++	–	8.5	6	165		Well—7 days
32 G. S.	+	+	1	3,150	+	+	++	–	9.6	94	530	255	Well—74 days
33 D. F.	?	+	1	3,980	+	++	–	–	15.0	42	365		Well—60 days
34 G. G.	–	+	17	3,720	–	+	+	–	5.8	24	135		Well—14 days
35 G. P.	–	+	3	2,480	–	++	++	–	9.5	5	235		Well—39 days
36 S. D.	–	+	31	3,010	–	++	++	–	1.5	6	125		Well—7 days
(2nd adm.)			45	3,080	–	+	–	–	9.0	0	140		Well—22 days
37 J. D.	+	+	6	1,800	+	+	+	–	2.0	37	555		Well—54 days
(2nd adm.)			101	3,720	–	++	–	–	9.2	0	155		Well—4 days
38 B. B.	+	+	NB	2,860	+	++	++	–	12.0	138	80		Died 2nd day
39 B. M.	–	+	8	3,600	+	++	–	–	10.2	0	120		Well—9 days
40 G. G.	?	0	2	2,980	+	+	–	–	14.1	0	180		Well—12 days
41 G. G.	+	+	1	3,300	+	+	–	–	13.0	2	170		Died 4th day
42 V. C.	–		19	3,480	++	++	++	–	8.3	5	120	120	Well—12 days
43 P. H.	–	0	2	2,300	+	+	++	+	12.7	7	140		Well—20 days
44 L. M.	–	+	1	3,040	++	+	+	–	11.5	122	701	205	Well—67 days
45 R. K.	?	+	40	3,920	–	+	+	–	6.5	0	380	230	Well—15 days
46 C. D.	–	+	1	3,080	+	+	–	–	9.0	68	225		Died 8th day
47 M. F.	+	+	1	4,130	+	–	++	+	18.5	110	415	235	Well—29 days
48 B. K.	–		1	2,760	++	++	++	+	15.4	37	40		Died 3rd day
49 G. S.		0	NB	2,250	+			++	–	–	–		Died 5 min.
50 G. C.	–	+	3	2,680	+	+	+	–	13.0	0	50		Died 4th day
51 P. S.	+	+	26	4,000	+	+	–	–	8.0	0	370		Well—11 days
52 C. B.	–	+	NB	3,000	++	–	++	+	10.5	150	447	447	Well—30 days
53 T. M.	–	+	25	3,500	–	–	–	–	6.8	6	260	80	Well—18 days
54 B. M.	–	+	11	4,090	+	+	–	–	10.0	0	195	195	Well—18 days
55 B. M.	–	+	1	3,760	+	++	+	+	4.0	1,900	150	150	Died 17 hrs.

*Key to abbreviations: FH = family history of hemolytic disease of the newborn.
Rh + means typical pattern, father and baby Rh positive and mother Rh negative.
Rh 0 means mother, father, and baby all Rh positive.
NB = Newborn.
Under Jaundice (and other symptoms) ++ means severe, + moderate, ? slight or doubtful, and – absent.

†A few of these cases were also reported by Javert.[4]

at birth. One died suddenly on the fifth day; the other (Case 37) was transferred to this hospital on the sixth day and responded well to transfusion therapy. The other eleven infants with positive family histories occurred as the second to eleventh pregnancies, with a total of nineteen previous infants manifesting hemolytic disease, eight abortions, and two stillbirths.

Of the forty-two patients who had no proved family history of hemolytic disease, the largest number, thirteen, occurred as the second pregnancy; ten, as the third; six, the fourth; four, the fifth; one, as the seventh; one, the ninth; and two, unknown. In addition to the first set of twins already mentioned, five occurred in the first pregnancy. Family histories of this group included nine spontaneous abortions, three stillbirths, and three babies dying early in the neonatal period.

Two of the infants (Cases 2 and 41) were children of a diabetic mother. They showed the typical findings including anemia and the characteristic Rh pattern: father's and babies' bloods were Rh positive; mother's blood, Rh negative. Hence, two factors may have contributed to the erythroblastosis in these infants, the effect of the maternal diabetes, described by Miller and Wilson,[5] and the isoimmunization mechanism.

In thirty-three cases, Rh factors were determined. Of these, twenty-eight (84 per cent) showed the typical pattern. In the remaining five (16 per cent), mother, father and infant were all Rh positive. These figures are consistent with the observations of others. Study of the family in which this disease was first manifested in the seventh pregnancy showed the father to be Rh positive; mother, Rh negative; first child, Rh positive; second child, Rh negative; third and fourth children, Rh positive; fifth, an abortion; sixth child, dead in infancy from meningitis; and the seventh child (Case 46), who had severe hemolytic disease resulting in death, Rh positive. In the two instances in which they were tested, the mothers' bloods were found to contain weak anti-Rh antibodies.

Clinical Picture.—Manifestations of the disease varied markedly in different infants. Most of the patients were visibly jaundiced at or soon after birth, with subsidence in some before admission to the hospital. The jaundice usually deepened for a few days, and depending on its severity took from one to eight weeks to clear. Comparison of the initial icterus index and corresponding hemoglobin in twenty-three cases in which both were determined showed no correlation (Fig. 1). The seven patients with less than 10 Gm. of hemoglobin per 100 c.c. of blood had icterus indices of less than 100, while the seven patients with icterus indices of 100 or more all had hemoglobin over 10 Gm. Repeated determinations in thirteen cases showed a progressive fall in icterus index unrelated to fluctuations in hemoglobin. This lack of correlation, to be discussed later, is contrary to the usual explanation that hemolysis is the chief cause of jaundice.

The liver was enlarged in forty-one cases, the spleen in thirty-two, ranging from slight enlargement to extension below the iliac crests. Both organs were usually firm and remained enlarged for several weeks.

The degree of anemia was also extremely variable. The initial hemoglobin was 8 Gm. or less in eleven cases, between 8 and 12 Gm. in thirteen cases, between 12 and 15 Gm. in fifteen, and over 15 Gm. in fourteen. In a few instances no anemia developed, but the usual course was one of gradually diminishing blood levels, despite repeated transfusions. Even the use of Rh-negative blood

did not prevent this tendency to recurrence of anemia. As seen in Fig. 1, the hemoglobin level had no constant relation to the degree of jaundice. In general, anemia tended to be most severe in babies admitted late. Only four infants with hemoglobin below 8 Gm. were admitted in the first week of life, while five were over 2 weeks old. Only one of the babies with severe anemia (hemoglobin less than 8 Gm.) died.

In almost every case in this series there was a moderate to marked increase in the number of nucleated erythrocytes seen in stained smears of peripheral blood. Only two of the eight infants in whom none were seen were under observation during the first week of life. Since the degree of erythroblastemia often decreases very rapidly, the fact that nucleated cells were not observed during hospitalization does not indicate that they had not been present at birth.

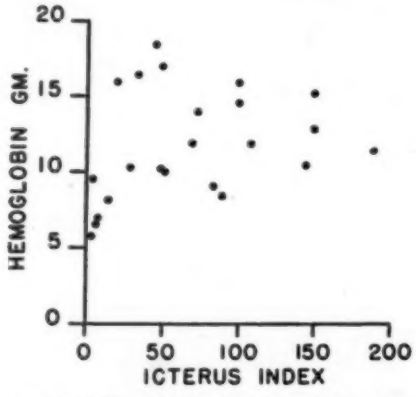

Fig. 1.—Comparison of initial hemoglobin and icterus index, showing no correlation.

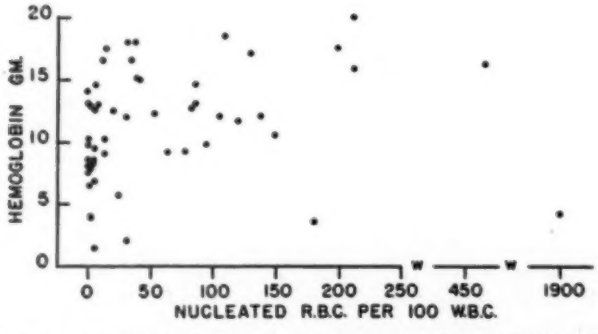

Fig. 2.—Comparison of number of nucleated red blood cells with hemoglobin level, showing lack of correlation.

There was no correlation between the degree of anemia and the number of nucleated red blood cells (Fig. 2).

An initially high number of nucleated erythrocytes was of poor prognostic import. The four babies with the highest number of such cells all died, and the mortality rate differed markedly in the groups with less and those with more than 50 nucleated red blood cells per 100 leucocytes (Table II). In babies who survived, the number of immature cells was maximum on the first or second day, decreased rapidly and disappeared on the average in about one week. This

TABLE II. MORTALITY ACCORDING TO NUMBER OF NUCLEATED ERYTHROCYTES

NO. NUCLEATED R.B.C.	NO. CASES	FATAL CASES	MORTALITY (%)
0-10	17	4	23
10-50	13	2	15
50-100	9	4	44
100+	13	6	46
Not recorded	3	3	

apparent regressive change in erythropoietic activity occurred in spite of anemia, which has been pointed out previously by Ross and Waugh.[6] In fatal cases the number of immature cells remained high or tended to increase. Persistent or increasing erythroblastemia was invariably a bad prognostic sign. This is illustrated by comparison of successive nucleated red blood cell counts in two fatal cases with one typical surviving one (Fig. 3).

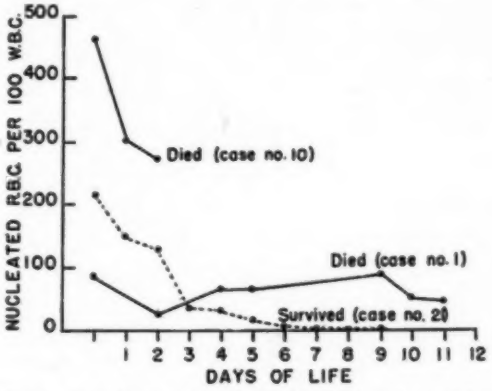

Fig. 3.—Trend of nucleated erythrocytes in fatal and surviving cases.

Edema was present in twelve infants, being severe with hydrops in only two, both of whom died. Marked edema is also recognized as a grave prognostic sign.

Hemorrhagic manifestations were noted in sixteen patients. The usual ones were petechiae, in thirteen; less frequent were bleeding from the gastrointestinal tract in five and from the genitourinary tract in four.

Special laboratory tests.—Prothrombin levels were determined in twenty-four cases. Of seven determinations done on the first three days of life in babies who had received no vitamin K, only two approached the normal range (70 per cent and 90 per cent, respectively, of adult normal values). The others were <5 per cent, <10 per cent, 20 per cent, 47.6 per cent, and 48 per cent. Three of the latter five showed hemorrhages, in contrast with the absence of hemorrhage in the two infants with higher prothrombin levels. During the first week of life prothrombin levels in twelve babies who had received from one to three doses of vitamin K (usually 2 mg. per dose by intramuscular injection) still tended to be low: <2 per cent, 7 per cent, 10 per cent, 25 per cent, 40 per cent, 42 per cent, 54 per cent, 61 per cent, 78 per cent, 79 per cent, 90 per cent, and 93 per cent of adult normal values. One-half of these patients had bleeding tendencies. In three babies whose mothers were given a course of vitamin K preceding delivery and who received vitamin K immediately after birth, initial prothrombin levels were 7 per cent, 14 per cent, and 51 per cent,

respectively, the third not having been determined until the twelfth day, after an additional dose of vitamin K had been given. When the initial prothrombin values were low, vitamin K tolerance tests showed a diminished response: 47.6 → 54 per cent; 2 per cent → 10 per cent; 35 per cent → 38 per cent. Table III shows the relationship of prothrombin levels and vitamin K therapy to the incidence of hemorrhage. Although the correlation is not perfect, the evidence is in favor of vitamin K deficiency as being one major cause, although not necessarily the only one, of hemorrhagic tendencies in patients with hemolytic disease of the newborn. As the other signs of the disease cleared, the prothrombin level tended to approach normal.

TABLE III. COMPARISON OF PROTHROMBIN LEVELS AND VITAMIN K THERAPY WITH INCIDENCE OF HEMORRHAGE[1]

CASE	DAY OF BIRTH	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6-10 DAYS	11-15 DAYS	16-20 DAYS	21-30 DAYS	31-40 DAYS	41-50 DAYS	51-60 DAYS
Cases With Hemorrhage												
27		**[2]		<2**10 Hem.				Hematemesis, death; autopsy showed hemorrhage, stomach				
12	<5 Hem.	**		Hem.		25		Petechiae at birth; bloody stool on 4th day				
21	**7 Hem.						34	Petechiae at birth				
11		<10	Hem.					Death; autopsy showed subarachnoid hemorrhage				
23		** Hem.	42			**	42	Petechiae on admission				
44		48**** Hem.		54	****	**93 **		Petechiae on admission				
48	Hem.	**** ****	61 Hem.					Petechiae, bleeding from rectum and penis at birth; autopsy—subarachnoid hemorrhage				
43			** Hem.		79			Petechiae on admission				
Cases Without Hemorrhage												
22		**		7	**				69			
16	****14			50				59**69	93			
25	20**			**			**			34		56
28	**	**		40								
39							44					
18		48										
26	**			**			51		34		35**38	
47		70*****		*****			81					
45											78	
52	**	78			*							
54	**						79					
51									80			
41		90**	93									
40				**		90						
15									100			

[1]Numbers represent prothrombin levels in per cent adult normal.
[2]Each * represents 1 mg. vitamin K.

Icterus indices varied between 0 and 440. The van den Bergh reaction was usually positive at the onset and predominantly indirect. As jaundice faded and the total van den Bergh decreased, the ratio of direct to indirect often increased, but did not reach 1 in the uncomplicated cases. The highest total van den Bergh was 119.2, coincident with the highest icterus index of 440.

Other than the response to vitamin K, no liver function tests were performed until late in the course of the illness. In Case 25, galactose tolerance test was normal on the thirty-fifth day, and bromsulfphthalein tests showed complete disappearance of the dye from the blood stream. In Case 26, bromsulf-

phthalein test on the fifty-second day revealed 20 per cent of the dye still in the blood after thirty minutes.

Total serum proteins were determined on many of the patients and showed no significant reduction, ranging between 5 and 7 Gm. per 100 c.c. serum. Fragility test was normal in each of the eight cases in which it was determined. Serologic tests for syphilis were negative in all patients.

Treatment.—The most important feature of treatment was transfusion, which was carried out in all but four patients. Prior to knowledge of the role of isoimmunization, parental blood was often used. The first transfusion of Rh-negative blood in this series was given in Case 17, in April, 1941, but Rh-negative blood did not become available for routine use until the summer of 1943. The usual transfusion consisted of 20 c.c. of whole citrated blood per kilogram of body weight (9 c.c. per pound), injected into a superficial vein at a rate of from 5 to 20 c.c. per minute.

For purposes of comparison the change in hemoglobin was employed as the most reliable and objective measure of the effect of a transfusion. The changes were estimated from the differences in hemoglobin values before and on the day after transfusion, or as soon thereafter as another determination was performed. When multiple transfusions were given between hemoglobin determinations, the total change was divided by the number of transfusions. Since varying amounts of blood were given, the increase in hemoglobin was corrected to the theoretical quantity if 20 c.c. per kilogram had been used by means of the following formula:

$$\text{Corrected increase in hemoglobin (Gm.)} = \frac{20 \times \text{observed increase} \times \text{wt. in kg.}}{\text{volume of transfusion (c.c.)}}$$

The few cases in which a fall in hemoglobin followed transfusion could not be corrected in this way; they were considered as negative values and included in the averages recorded in Tables IV and V.

TABLE IV. RISE IN HEMOGLOBIN RESULTING FROM TRANSFUSIONS WITH BLOOD OF RH-POSITIVE, RH-NEGATIVE, AND UNKNOWN COMPOSITION, BASED ON TRANSFUSION OF 20 C.C. PER KILOGRAM BODY WEIGHT

AGE OF PATIENT	RH-POSITIVE BLOOD		RH UNKNOWN		RH-NEGATIVE BLOOD	
	NO. TRANSFUSIONS	AVERAGE RISE HEMOGLOBIN/ TRANSFUSION (GM.)	NO. TRANSFUSIONS	AVERAGE RISE HEMOGLOBIN/ TRANSFUSION (GM.)	NO. TRANSFUSIONS	AVERAGE RISE HEMOGLOBIN/ TRANSFUSION (GM.)
0 to 6 days	10	1.5	50	1.3	18	1.3
7 to 13 days	3	0.7	37	1.5	7	1.4
14 days+	8	1.8	86	1.6	15	1.8
Total	21	1.5	173	1.5	40	1.5

TABLE V. DECREASING EFFECT OF TRANSFUSIONS AT HIGHER HEMOGLOBIN LEVELS

INITIAL HEMOGLOBIN	RH-POSITIVE BLOOD		RH UNKNOWN		RH-NEGATIVE BLOOD	
	NO. TRANSFUSIONS	AVERAGE RISE HEMOGLOBIN/ TRANSFUSION (GM.)	NO. TRANSFUSIONS	AVERAGE RISE HEMOGLOBIN/ TRANSFUSION (GM.)	NO. TRANSFUSIONS	AVERAGE RISE HEMOGLOBIN/ TRANSFUSION (GM.)
0 to 7.9 Gm.	1	3.5	24	2.4	3	0.5
8 to 12.9 Gm.	12	1.1	110	1.4	21	2.2
13 Gm.+	8	1.9	39	1.2	16	0.8
Total	21	1.5	173	1.5	40	1.5

The majority of transfusions, even those of Rh-positive blood, were followed by good immediate response both in raising the hemoglobin level and in improving the clinical condition of the patient. Twenty-eight transfusions were given with known Rh-positive blood, or with fathers' blood, which presumably contained the Rh factor. Three patients, receiving five transfusions, died before a second blood count was made. These were all in poor condition on admission—weak, cyanotic, or comatose—and there was no indication that transfusion precipitated death. There was only one definite transfusion reaction, with fever, jaundice, and hematuria following transfusion with 75 c.c. of father's blood. Two additional transfusions of 50 c.c. of the father's blood were, however, without ill effect and resulted in a satisfactory rise of hemoglobin.

Because the expected response to transfusion varies with age, the transfusions were arbitrarily divided into age groups of 0 to 6 days, 7 to 13 days, and 14 days and over. The average increase in hemoglobin resulting from ten transfusions of Rh-positive blood given during the first week of life was 1.5 Gm. (Table IV). The average from all the twenty-one transfusions was also 1.5 Gm.

Mother's blood was used for five transfusions in two babies from 5 to 7 days old, with rises in hemoglobin of 1.3 Gm., 2.0 Gm., and 3.0 Gm. No ill effects were noted. The mothers' titers of anti-Rh antibodies must have been low in these instances.

Forty transfusions were given with Rh-negative blood. One in a severe case of hemolytic disease (Case 55) was followed by cyanosis, bloody mucoid nasal discharge, hematuria, and death in forty-eight hours. There were no other evidences of transfusion reaction. Following eighteen transfusions given during the first week of life the average rise in hemoglobin was 1.3 Gm. The average for the entire series of forty transfusions was 1.5 Gm. (Table III).

One hundred seventy-three transfusions were given with blood of unknown Rh composition, of which from 80 to 90 per cent might be expected to be Rh positive. In two cases death followed transfusions and may have been precipitated by them. In Case 10, the infant was progressing satisfactorily until the fourth day, except that the number of nucleated red blood cells remained in excess of 200 per 100 leucocytes. Repeated daily transfusions from the same donor were given although the hemoglobin did not fall below 15.5 Gm. On the fourth day there was suddenly cyanosis, bloody vomitus, bloody urine, rapidly increasing hepatosplenomegaly, and death. Autopsy showed hemosiderin in the renal tubules as well as extramedullary hematopoiesis and bronchopneumonia. The other patient (Case 46) was moderately anemic at birth. The hemoglobin fluctuated between 9 and 11.8 Gm., and the baby's clinical condition was good until the eighth day, about forty hours after the last transfusion, when she suddenly became limp and pale and died within an hour. Hemoglobin on the morning of death was 6.9 Gm. Death appeared to be caused by a hemolytic crisis either because of or in spite of transfusion.* In four infants jaundice became more intense after transfusion. In Case 16, jaundice appeared after the first transfusion, and the liver and spleen became markedly larger. In Case 18, there were two minor reactions, fever of 39.6° C. on the tenth day and transient hematuria on the fifty-second day, after the eighteenth transfusion. The average rise of hemoglobin following the fifty transfusions given during the first week of life was 1.3 Gm. The average for all the 173 transfusions was 1.5 Gm. (Table IV).

*Blood used for these transfusions was obtained from another hospital as Rh-negative blood, but when retested after the infant's death by our Blood Bank, the report was Rh positive. In view of this discrepancy, it was included in the group of transfusions of blood of unknown Rh composition.

Although little difference was noted in the response to Rh-negative and Rh-positive blood by this criterion, follow-up studies showed that the rise of hemoglobin tended to be better sustained after transfusions of Rh-negative blood. Two patients, similar to those reported by Brown and Levine[7] and Wiener and Wexler,[8] became temporarily Rh negative after several Rh-negative blood transfusions.

The response to transfusion varied also according to the initial hemoglobin level. There was a tendency to decreasing benefit with increase of the initial hemoglobin level (Table V). However, our results did not demonstrate a definite optimal level above which further transfusions were unwarranted.

The mortality of patients treated with each type of blood is indicated in Table VI. The striking lowering of mortality as recorded for the Rh-negative

TABLE VI. MORTALITY OF PATIENTS ACCORDING TO TYPE OF BLOOD USED IN TRANSFUSIONS*

TYPE BLOOD	NO. PATIENTS	NO. FATAL	MORTALITY (%)
Rh+ or father's blood	10	3	30
Mother's blood	2	0	0
Rh unknown	42	12	29
Rh-negative	12	1	8

*Since some of the patients received transfusions of more than one kind of blood, they are included in two or more groups, which explains why the total number of patients in this table appears greater than the number of infants under study.

group was unfairly weighted, however, by the fact that two newborn babies admitted recently in poor condition were given bank blood and died before Rh-negative blood could be obtained. Both these babies would undoubtedly have died even if Rh-negative blood had been immediately available, since both had massive internal hemorrhages.

Therapy in addition to transfusions varied from patient to patient. During the past year a high carbohydrate, high protein, low fat formula, made from powdered half-skimmed milk, has been used. Nearly all the patients received vitamin K intramuscularly in repeated dosage until the prothrombin time became normal. Infants who were not anemic were frequently given plasma infusions. Some of the patients were given intramuscular injections of crude liver extract. Recently, choline chloride, 0.3 Gm. daily, has been given orally, as recommended by Danis and Anderson.[9] The course of the illness has not been significantly altered by either of these agents, but they have not yet been given an adequate trial.

Course.—Recovery from the disease required from one week to three months. In severe cases, the jaundice cleared slowly, the skin taking on a rather ghastly shade of green before all the bile pigment was resorbed. The tendency for anemia to recur often lasted as long as from four to six weeks after birth, necessitating repeated transfusions. Three patients had second hospital admissions for this reason. Three other patients developed an obstructive type of jaundice in the second week, stools becoming white, urine dark, and van den Bergh test strongly positive in an immediate direct reaction. All three had been repeatedly transfused with blood of unknown Rh composition, although none was anemic. One (Case 25) cleared completely; another (Case 26) still had impairment of liver function as indicated by bromsulfphthalein and vitamin K tolerance tests at the time of discharge; the third (Case 16) was improving when he contracted a urinary tract infection and died of *Bacillus coli* sepsis.

TABLE VII.

CASE	AGE AT DEATH	WT. (GM.)	LIVER	SPLEEN	KIDNEYS	ADRENAL	AUTOPS
1	12 days	4,820	203 Gm.; increased fibrous tissue; necrosis; diffuse hematopoiesis	10 Gm.; diffuse marked hematopoiesis		2 large areas necrosis with hemorrhage; moderate areas hematopoiesis	Slight
7	7 days	3,900	176 Gm.; numerous foci hematopoiesis	22 Gm.; congestion, free pigment; few foci hematopoiesis			
8	3 days	term	174 Gm.; numerous areas hematopoiesis	27 Gm.; many tiny areas hematopoiesis	Many small foci hematopoiesis		Hypertro
10	4 days	3,000	162 Gm.; cells granular and vacuolated; hematopoiesis	12.5 Gm.; congestion; foci of hematopoiesis	Iron pigment in tubules	Hematopoiesis in inner part	
11	3 days	2,460	133 Gm.; pale, extensive fatty degeneration; congestion; moderate number hematopoietic foci	8 Gm.; moderate congestion	Moderate congestion	Moderate congestion	Hypertro ventricl
13	3 days	2,080	72 Gm.; large areas necrosis; usual foci hematopoiesis	6 Gm.; congestion; large follicles; usual hematopoiesis		Many cortical cells with elongated clefts having sharp borders; large areas lipoid in cortex	Hypertro
16	30 days	3,620	230 Gm.; hepatic cells edematous; bile thrombi; several foci of hematopoiesis	30 Gm.; congestion; large phagocytes with R.B.C.; pulp increased	Many abscesses		Blood cys tricuspid
20	4 days	2,220	88 Gm.; pigment granules; large amount hematopoietic tissue	18 Gm.; malpighian bodies slightly hyperactive; small islets hematopoiesis			
27	4 days	3,980	200 Gm.; hematopoiesis	36 Gm.; large germinal follicles; small areas myelogenesis	Small submucous hemorrhages scattered areas myelogenesis	Small hemorrhage cortex and medulla; congestion	Blood cys tricuspid
30	4 hr.	2,700	110 Gm.; large foci hematopoiesis	12 Gm.; small foci hematopoiesis			
38	2 days	2,860	161 Gm.; considerable hematopoiesis	47 Gm.	Congestion; bile pigment in tubules		Hypertropl Blood cys valve
41	4 days	3,280	215 Gm.; numerous foci hematopoiesis	25 Gm.; focal abscesses		Necrotic cells in androgenic zone	
46	8 days	3,040	220 Gm.; numerous foci hematopoiesis, fat vacuoles and yellow pigment	39 Gm.; numerous foci hematopoiesis	Cells of proximal convoluted tubules swollen		

AUTOPSY FINDINGS

HEART	LUNGS	BRAIN	OTHER
Slight hypertrophy	Partial atelectasis		Subcutaneous edema; small pleural and pericardial effusion and ascites; erythrocytic and granulocytic hyperplasia of marrow
	Bronchopneumonia	Infarction and cystic degeneration of choroid plexus	Marked edema, ascites, and pericardial effusion; mongolism; active hematopoiesis of thymus; marrow hyperplastic
Hypertrophy	Bronchopneumonia	Kernicterus, slight	Petechiae bladder and uterus; few small areas of hematopoiesis in pancreas
	Fibrinous bronchitis; bronchopneumonia with hemorrhage		Marrow hyperplastic; edema; lymphoid follicles in pancreas
Hypertrophy right ventricle	Some gastric contents in trachea; bronchopneumonia	Subarachnoid hemorrhage; softening right parietal cortex	
Hypertrophy	Numerous areas atelectasis and hemorrhage		Placenta showed single ovum twins with fibrinoid degeneration and calcification beneath choroid plate
Blood cysts of tricuspid valve	Bronchopneumonia	Purulent leptomeningitis	Ascites; pleural effusion
	Subpleural and interstitial hemorrhage; extracellular yellow-brown granules	Kernicterus, slight	Hyperplastic marrow; small foci hematopoiesis in pancreas
Blood cysts of tricuspid valve	Partial atelectasis; small hemorrhages	Kernicterus, marked	Large areas of hemorrhage in stomach, colon; pseudoesophagitis
	Moderate atelectasis	Subarachnoid hemorrhage; congestion pia-arachnoid	
Hypertrophy; few blood cysts on mitral valve	Considerable yellow pigment in bronchioles and alveoli	Moderate congestion; slight kernicterus	Petechiae intestine; marrow hyperplastic
	Aspiration bronchopneumonia; hemorrhage in alveoli		Septicemia, hemolytic *Staphylococcus aureus*
			Slight pleural and pericardial effusions, ascites; many small subserosal hemorrhages in intestine; densely cellular marrow

(TABLE VII—CONT'D)

CASE	AGE AT DEATH	WT. (GM.)	LIVER	SPLEEN	KIDNEYS	ADRENAL
48	3 days	2,760	220 Gm.; filled with hematopoietic tissue	50 Gm.; small foci hematopoiesis	Few areas of hematopoiesis	Slight hemorrhage and degeneration intermediate zone; small foci hematopoiesis
49	5 min.	2,250	118 Gm.; hematopoietic foci one-half bulk of liver	21 Gm.; many foci hematopoiesis; prominent sinusoids	Scattered areas hematopoiesis	Many vacuoles in boundary zone cells
50	4 days	2,680	160 Gm.; fat vacuoles; moderate number small foci hematopoiesis	15 Gm.; reticulum cells hyperplastic; focal areas hematopoiesis	Yellow pigment in tubules	Cortex edematous; few tiny foci hematopoiesis
55	17 hr.	3,670	220 Gm.; large foci hematopoiesis; gold-brown pigment	45 Gm.; small foci hematopoiesis	Few foci of hematopoiesis	Few foci of hematopoiesis

The most frequent complication was diarrhea. Of the forty-three infants who survived more than four days, 19 (44 per cent) developed a nonspecific watery diarrhea, usually mild, occasionally causing mild acidosis, and responding promptly to a brief period of starvation and parenteral fluid therapy. This complication occurred in spite of a pavilion in which each baby had its own cubicle, and in which the development of diarrhea in patients admitted for other causes was extremely rare. This complication was discussed by Darrow[10] but is seldom mentioned in the recent literature.

Only one of the surviving babies had neurological residua—spasticity and mental retardation—attributed to kernicterus.

Mortality.—Nineteen of the fifty-five infants died, a mortality of 35 per cent. In the cases ending fatally the babies usually succumbed within the first two or three days. Only four babies died who were in good condition on admission: one from aspiration pneumonia, one from septicemia, and two from possible transfusion reactions or hemolytic crises. These four might have been saved with Rh-negative blood and modern chemotherapy. Of the remainder, four were premature (2,080 to 2,460 Gm.) and one a fetal hydrops, who breathed only a few times. These and the other eleven full-term babies were extremely ill from the start, cyanotic, limp, jittery, with shallow respirations, poor activity, weak or high-pitched cry, occasionally comatose or moribund. From the onset they obviously had little or no chance for recovery. Although some of the infants who recovered were described as listless, lethargic, or slightly cyanotic, none was in such poor condition as those who died. In nine of the fatal cases there were petechiae or other hemorrhagic manifestations before death. With the exception of Case 55 (4.0 Gm. hemoglobin), there were in the fatal cases normal or only slightly diminished hemoglobin values on admission, ranging from 9 to 23 Gm. with an average of 13.7 Gm. The final hemoglobin values in these patients varied from 6 to 22.5 Gm. with an average of 13 Gm., and only three were under 11 Gm. Thus, anemia did not appear to be a major cause of death.

Autopsies were performed in seventeen of the nineteen fatal cases (Table VII). All showed extramedullary hematopoiesis, invariably in the liver, almost

(CONT'D)

HEART	LUNGS	BRAIN	OTHER
	Collapsed; fluid in alveoli	Subarachnoid hemorrhage with clots around base of brain	Hemorrhages skin, petechiae intestine; marrow very cellular, mainly erythropoiesis; islets of pancreas rather large; small foci hematopoiesis in pancreas
	Atelectasis		Ascites
	Vernix and hemorrhage in alveoli	Kernicterus	Hemorrhage in stomach; fibrinous esophagitis; marked erythroblastic hyperplasia of marrow
	Hemorrhages in pleura; blood and edema fluid in alveoli		Edema; few areas of hematopoiesis in thymus; marrow hyperplastic; scattered petechial hemorrhages

constantly in the spleen, and frequently in the kidneys, adrenals, pancreas, and thymus. Five patients had hemorrhages of sufficient severity to account for death, either intracranial or gastrointestinal. Eight others exhibited hemorrhages of lesser magnitude. Two infants died of infection, one of the urinary tract, the other a hemolytic *Staphylococcus aureus* septicemia secondary to aspiration pneumonia. The cause of death was not obvious in the other patients. Many had varying degrees of atelectasis and/or bronchopneumonia. Five had cardiac hypertrophy. Nine showed necrosis, fatty degeneration, or unusual pigmentation of the liver. Four had small areas of hemorrhage or necrosis in the adrenals. One showed slight hypertrophy of the islets of Langerhans. Five had kernicterus, one of which was severe. Intrauterine asphyxia is one possible contributing cause of death, as suggested by Rothman and Hopkins.[11]

DISCUSSION

The pathogenesis of hemolytic disease of the newborn has not yet been completely elucidated. The factor of isoimmunization has been generally accepted and needs no repetition. But the mechanism by which the Rh antigen-antibody reaction brings about the various manifestations of the syndrome is not clear. Recent papers stress hemolysis as the primary factor with the other manifestations as secondary to the hemolysis and the accompanying anemia. Potter[3] stated, "Erythroblastosis fetalis is a disease characterized by the abnormal destruction and regeneration of erythrocytes. . . . The pathologic manifestations of erythroblastosis are direct results of excessive destruction of erythrocytes and of an attempt on the part of the body to compensate for this loss."

It is difficult to reconcile the findings in some of our patients with this sequence of events. In Case 47 there was slight jaundice at birth (icterus index, 45), definite hepatosplenomegaly, and 110 nucleated erythrocytes per 100 leucocytes; yet the hemoglobin was 18.5 Gm. Later, when the hemoglobin dropped to 10 Gm., the icterus index also fell to 10.8. Hemolysis obviously did not increase the jaundice. In Case 28 there was jaundice, hepatosplenomegaly, and 131 nucleated red blood cells at birth with a hemoglobin of 17 Gm. In Case 21

there was hepatosplenomegaly, slight edema, and 214 nucleated cells with 16 Gm. of hemoglobin. How can one postulate in these cases enough hemolysis to cause jaundice or enough anemia to be responsible for the enlarged liver and spleen and the erythroblastemia? On the other hand, one patient (Case 14) was admitted on the sixth day with a hemoglobin of 4 Gm., only 2 nucleated red blood cells, and moderate jaundice. Another patient (Case 37), also 6 days old on admission, had 2 Gm. of hemoglobin, 380,000 red blood cells, yet only 37 nucleated erythrocytes per 100 leucocytes. If anemia stimulates erythroblastosis, one might expect more immature forms in these cases of severe anemia. Moreover, it is commonly observed that the fall in hemoglobin during the first few days of life is accompanied by a decline in nucleated red cells. Therefore it is difficult to maintain that anemia is solely or primarily responsible for erythroblastemia.

Since jaundice may be present at birth before anemia has developed, it seems likely that impairment of liver function exists in these patients. Cases of jaundice without anemia similar to ours have been reported by Hoffmann and Hausmann,[12] Astrachan,[13] and Hellman and Hertig.[14] Graham[15] in 1912 described fatty infiltration and degeneration in the liver of infants dying of this condition, and produced similar changes in the livers of fetal animals by asphyxia, induced mechanically or by anesthesia. Ylppö[16] ascribed the jaundice of icterus gravis neonatorum solely to hepatic dysfunction. Additional evidence of poor liver function includes disturbance of carbohydrate metabolism,[17] macrocytic type of anemia,[18] poor prothrombin formation,[9] and postmortem findings of fatty degeneration and necrosis of the liver.[4, 10, 14, 15, 17, 19, 20, 21] Impaired ability of the liver to form prothrombin has been amply demonstrated in this study. Prenatal administration to the mother of vitamin K supplemented by an additional dose to the baby at birth resulted in prothrombin levels in two babies of less than 15 per cent; more than one-half the babies showed less than the expected response to vitamin K in raising prothrombin levels. The autopsy findings in nine patients of this series showed liver damage, with necrosis, fatty degeneration, vacuolation, or unusual pigment accumulations.

A number of explanations have been advanced for the cause of this poor liver function. Compression of liver cells by erythropoietic tissue was refuted by Abt[21] on the ground that similar overcrowding in leucemia and Niemann-Pick disease did not cause hepatic damage. Other possibilities are intrauterine asphyxia due to placental abnormality[13] or to drugs given the mother in labor, immaturity, constitutional inferiority, or anaphylaxis. Darrow,[10] even before the development of Rh studies, suggested that the observed hepatic damage, as well as the entire clinical picture of hemolytic disease of the newborn, might be explained on the basis of a hypothetic antigen-antibody reaction due to transplacental immunization of the mother. Focal necroses of liver have been produced experimentally in sensitized rabbits and guinea pigs by Hartley and Lushbaugh[22] by the injection of sublethal doses of antigenic serum. Reisner[18] suggested that the liver damage in erythroblastosis fetalis as well as the hemolysis might be caused by the antigen-antibody reaction. In view of the extensive hepatic damage in fetal hydrops and less severe changes in hemolytic disease, he suggested that fetal hydrops, icterus gravis, and congenital anemia represented respectively severe, moderate, and mild antigen-antibody reactions.

On the basis of a poorly functioning liver, jaundice could occur without hemolysis, and a minor degree of hemolysis would increase the jaundice because

of inability of the liver to excrete all the bile pigment. Anoxia secondary to anemia would aggravate the liver damage, and obstruction of bile canaliculi with inspissated bile might lead to an obstructive type of jaundice. Since the degree of liver damage is variable, the cases of so-called congenital anemia without icterus probably represent instances in which liver function is sufficiently good for excretion of bile pigment as it is liberated by hemolysis.

Treatment at present relies mainly on transfusions with Rh-negative blood. Recent papers have stressed the urgency of its use. Gimson[23] concluded that an infant born with jaundice with a family history of hemolytic disease should be transfused immediately with Rh-negative blood, irrespective of erythrocyte and hemoglobin levels. Wiener and Wexler[8] advised immediate transfusion, repeated in twenty-four hours, in an attempt to forestall possible hemorrhagic symptoms. Davidsohn[24] said it was important to give blood as early as possible. Potter[25] also recommended prompt transfusion: "In the group who do not show an appreciable anemia at birth, transfusion still seems to improve the chance of survival. The infant appears to be benefited by the introduction of cells which are incapable of being affected by the antibodies producing the disease." Mollinson[26] suggested that early and adequate transfusion might lower the incidence of damage to the central nervous system.

When anemia is present at the time the infant comes under observation, there is no question that prompt transfusion is advisable. Mollinson's[27] results on the relative survival of Rh-positive and Rh-negative erythrocytes after mixed transfusions confirm the clinical evidence that Rh-negative blood is preferable during the first two weeks of life. When the baby is not anemic, the advisability of immediate transfusion may be questioned. What does one hope to gain by transfusing a patient who has a normal hemoglobin? Is it not possible to increase the load on an already poorly functioning liver by overloading the circulation with unneeded erythrocytes? May not obstructive jaundice, presumably due to inspissated bile, be induced by unnecessary transfusions? Might too many transfusions add to the dangers of kernicterus, a possibility suggested by Potter? Anemia in itself is rarely if ever a cause of death in these babies if they are under careful observation. In our experience, it has never developed so rapidly that daily blood counts did not provide ample time to institute transfusion therapy. Perhaps we have been overzealous with transfusions. Besides the possible causation of obstructive jaundice, the extra handling required and the frequent trips to the treatment room may have been partly responsible for the unusually high incidence of diarrhea. Since the same amount of blood has a greater and more lasting effect the older the patient is, it is a saving of blood, of trauma to the baby, and of the time of the house staff to postpone transfusions until they are more definitely indicated.

Because the main benefit of transfusions in babies who are not anemic is prevention of possible hemorrhagic tendencies, a benefit derived from the plasma rather than the erythrocytes, plasma infusion in these babies is preferable to whole blood. It is advantageous not only in the avoidance of most of the possible bad effects of whole blood transfusions, but also because of its ready accessibility without the necessity of blood typing and cross matching.

On the basis of our observations, the following policy is suggested. Patients in good general condition without anemia or hemorrhagic manifestations are not transfused at once. Hemoglobin determinations are done twice daily and

erythrocyte and differential counts once daily for the first ten days, then less frequently as indicated. Transfusions of Rh-negative blood are given as soon as anemia develops, the threshold being a blood level of 11 Gm. of hemoglobin. This is an arbitrary level, chosen to give an adequate margin of safety without encouraging unnecessary transfusions. Occasional plasma infusions are given in this group during the first week. Infants in critical condition or with bleeding tendencies, even in the absence of anemia, are given small transfusions of freshly drawn Rh-negative blood for its supportive effect and for aid in stopping bleeding.

The rationale of vitamin K therapy has been demonstrated. However, it has been our experience as well as that of others that the effect of vitamin K on the prothrombin level is often slight and delayed, probably because the poorly functioning liver is unable to convert it to prothrombin. Even giving vitamin K to the mother in three instances led to disappointingly low levels in the baby. Another measure which has theoretical advantage is the administration of vitamin K to Rh-negative donors before withdrawal of blood. The results of Kinsey[28] in combatting the low prothrombin levels and hemorrhagic tendencies in severe liver damage by transfusions from donors who had been fortified with vitamin K encourage the belief that the same measure might be of benefit in hemolytic disease of the newborn. If so, it would be of great importance in view of the high incidence of hemorrhage as a cause of death.

Because of the evidence of liver damage, a high protein, high carbohydrate, low fat diet, as well as liver extract and choline, warrant further trial.

CONCLUSIONS

1. Fifty-five cases of hemolytic disease of the newborn treated at the New York Hospital in the six years, 1938-1944, have been summarized. (a) The clinical picture was extremely varied; jaundice, anemia, degree of erythroblastemia, and hemorrhagic manifestations varied independently. (b) A high incidence (44 per cent) of nonspecific diarrhea was noted. (c) The effects of transfusion with Rh-positive, Rh-negative blood, and bank blood not typed for Rh factor were compared. Immediate results following transfusion in raising hemoglobin and improving clinical condition were equally good, but Rh-negative blood transfusions caused a better sustained rise in hemoglobin, fewer reactions, and lower mortality. (d) Nineteen infants died, a mortality of 34 per cent. One of the chief causes of death was hemorrhage.

2. Jaundice out of proportion to or in the absence of anemia was attributed to impaired liver function. This thesis was supported by low prothrombin levels responding poorly to vitamin K administration, pathologic findings of fatty degeneration and necrosis of the liver, and evidence obtained from the literature.

3. The necessity for immediate transfusion in the presence of normal blood levels was questioned, and reasons were given for delaying transfusion until anemia impends. Plasma infusions were preferred in this type of patient.

4. The prominence of hemorrhagic tendencies in patients with hemolytic disease of the newborn was emphasized and its relation to low prothrombin levels demonstrated.

5. Administration of vitamin K to donors of Rh-negative blood was suggested as a means of raising the prothrombin levels of affected infants.

REFERENCES

1. Landsteiner, K., and Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. 43: 223, 1940.
2. Levine, P., Katzin, E. M., and Burnham, L.: J. A. M. A. 116: 825, 1941.
3. Potter, E. L.: Am. J. Dis. Child. 68: 32, 1944.
4. Javert, C. T.: Surg., Gynec. & Obst. 74: 1, 1942.
5. Miller, H. C., and Wilson, H. M.: J. PEDIAT. 23: 251, 1943.
6. Ress, S. G., and Waugh, T. R.: Am. J. Dis. Child. 51: 1059, 1936.
7. Brown, H. R., and Levine, P.: J. PEDIAT. 23: 290, 1943.
8. Wiener, A. S., and Wexler, I. B.: Am. J. Clin. Path. 13: 393, 1943.
9. Danis, P. G., and Anderson, W. A. D.: South. M. J. 35: 1070, 1942.
10. Darrow, R. R.: Arch. Path. 25: 378, 1938.
11. Rothman, P. E., and Hopkins, H.: Am. J. Obst. and Gynec. 45: 291, 1943.
12. Hoffmann, W., and Hausmann, M.: Monatschr. f. Kinderh. 33: 193, 1926, cited by Zuelzer.[17]
13. Astrachan, M.: Am. J. Dis. Child. 53: 541, 1937.
14. Hellman, L. M., and Hertig, A. T.: Am. J. Obst. & Gynec. 36: 137, 1938.
15. Graham, E. A.: J. Exper. Med. 15: 307, 1912.
16. Ylppö, A.: Ztschr. f. Kinderh. 17: 334, 1918, cited by Zuelzer.[17]
17. Zuelzer, W. W., and Bigler, J. A.: Am. J. Dis. Child. 60: 873, 1940.
18. Reisner, E. H.: Arch. Int. Med. 71: 230, 1943.
19. Polayes, S. H.: Pathology of Erythroblastosis Fetalis, read at a meeting of the New York Pathological Society, New York Academy of Medicine, Jan. 22, 1942, cited by Reisner.[18]
20. Hawksley, J. C., and Lightwood, R.: Quart. J. Med. 27: 155, 1934.
21. Abt, A. F.: J. PEDIAT. 3: 7, 1933.
22. Hartley, G., and Lushbaugh, C. C.: Am. J. Path. 18: 323, 1942.
23. Gimson, J.: Brit. M. J. 2: 293, 1943.
24. Davidsohn, I.: M. Clin. North America 28: 232, 1944.
25. Potter, E. L.: M. Clin. North America 28: 254, 1944.
26. Mollinson, P. L.: Proc. Roy. Soc. Med. 36: 221, 1943.
27. Mollinson, P. L.: Arch. Dis. Childhood 18: 161, 1943.
28. Kinsey, R. E.: Arch. Int. Med. 73: 131, 1944.

ANEMIA OF THE NEWBORN

A Case Report

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THE many textbooks on pediatrics and reports appearing in the current literature continue to be confusing and are often conflicting in the classification of anemia of the newborn. Too often in the cases reported the etiology is not determined. Consequently no definite preventive measures can be considered and employed. I feel fairly certain that if the many unusual cases which occur are reported, and if a careful analysis of them is made, in the course of time it will aid materially in clarifying and solving the problem of that all-inclusive condition termed anemia of the newborn. It is with this thought in mind that the following case report is recorded.

This full-term male was normally delivered on Nov. 19, 1943. There was one other child in the family, and the family history was entirely negative. At birth the baby presented no abnormalities. The birth weight was 6 pounds, 12 ounces. About one hour after birth patient was given an injection of vitamin K* this being done routinely to prevent hypoprothrombinemia. From the time of birth the baby appeared slightly pale but otherwise normal. On November 24 and 25 the mother noticed that the baby had slight momentary and fleeting twitchings of the left arm and left leg. An examination was entirely negative, except for the previously mentioned slight pallor. On November 26 the baby had generalized

From Bushnell General Hospital, Brigham City, Utah.

*Hykinone, 1 c.c. (Abbott Laboratories, North Chicago, Ill.)

clonic convulsions with slight cyanosis. Following the seizures he appeared extremely and ghastly pale, but examination otherwise was negative. At this time urine, blood calcium, leucocyte count, bleeding and clotting times, and red blood cell morphology were normal, but the red blood cell count was 1.54 million. The baby was given 65 c.c. of citrated blood intravenously. On November 27 and 29 the baby was again transfused with 80 c.c. of citrated blood on each day. Following the transfusions the baby's color became a normal pink and he appeared perfectly well. There was no jaundice, no enlargement of the liver or spleen, and no adenopathy. He took his feedings well, gained weight, and had normal stools. He was sent home on an evaporated milk-Karo formula, orange juice, oleum percomorphum, and ferrous carbonate, 10 grains daily.

Despite an apparent state of well-being, the baby's erythrocyte count underwent a gradual decrease to 2.48 million on December 16. On this date he was given a transfusion of 75 c.c. of citrated blood. On December 23 liver extract, ½ c.c., was begun every other day. On December 30 the red blood cell count was 3.15 million. On Jan. 3, 1944, 100 c.c. of citrated blood was given. On January 15 the erythrocyte count was 4.33 million, but by February 1 it had dropped to 3.29 million. On February 2 another transfusion was given. From this time on the baby's color remained good, and his general condition progressed most satisfactorily. On April 25 the red blood cell count was 4.29 million. On May 1 the liver extract was decreased to ½ c.c. twice weekly and on July 1 to once weekly, then discontinued on August 1. On July 7 the red blood cell count was 4.18 million, on September 5 3.91 million and finally on November 14 4.06 million. Complete laboratory findings covering a period of one year are recorded in Table I.

TABLE I

LABORATORY FINDINGS AND BLOOD TRANSFUSIONS

DATE	R.B.C.	HB.	W.B.C.	P.*	L.	M.	E.	R.	PLATELETS	COAG. TIME	BLEEDING TIME	BLOOD CALCIUM	Rh	R.B.C. (FR.)†	TRANSFUSIONS
11/26/43	1.54	6.9	12,150	75	20	1	4			6 min.	5 min.	12.5			65 c.c.; donor Rh positive
11/27/43															80 c.c.; donor Rh positive
11/28/43	3.08		6,650												
11/29/43															80 c.c.; donor Rh positive
12/ 1/43	4.02	12	15,300	21	79										
12/ 4/43	3.25	11	11,000	35	51	5	9								
12/ 7/43	3.45	11.4	13,050												
12/16/43	2.93	10	11,200												
12/20/43	2.48	7.6	9,700	36	64			4.3	380,000						75 c.c.; donor Rh positive
12/30/43	3.15	8.8	6,800	22	76	2		0.4							
1/ 3/44															100 c.c.; donor Rh positive
1/15/44	4.33	12.4	7,750	21	76	1	2		150,000						
2/ 1/44	3.29	10	5,900	7	85	6	2						Pos.	.46 .34	
2/ 2/44															100 c.c.; donor Rh negative
4/25/44	4.29	12	11,200	13	82	3	2	1.7	195,000						
7/ 7/44	4.18	11.8	10,300	12	75	4	2	0.2	135,000				Pos.		
9/ 5/44	3.91	12.8	11,600	13	84	3		0.1	164,000						
11/14/44	4.06	13	13,400	27	69	2	2	0.1	250,000						

*P., polymorphonuclears; L., lymphocytes; M., monocytes; E., eosinophiles, R., reticulocytes.
†FR., fragility.

COMMENT

The patient's convulsions are explained on the basis of anoxemia secondary to marked anemia.

The father was Rh positive; mother, Rh negative; and the baby, Rh positive. However, it does not seem likely that the Rh factor had any etiological significance in this case, since there were no nucleated red blood cells in the peripheral circulation and there was no evidence of hemolysis such as jaundice

or blood in the urine. There was no demonstrable hemorrhage or petechiae. There was no increase in the bleeding or clotting times. There was no evidence of cord infection and no fever. The serology of the patient's mother and father was negative. Fragility of the red blood cells was normal.

The baby was maintained for two and one-half months on transfused blood until he was apparently able to generate a normal amount of his own blood. It is felt that the iron and liver extract probably had no particular influence on the course of the disorder. At the end of one year the baby was normal and thriving.

SUMMARY

A case of anemia of the newborn, which might be classified as congenital hypoplastic anemia, including laboratory findings and follow-up for one year, is reported. It adds one more case to those which have been previously recorded.

STAPHYLOCOCCUS ALBUS HEMOLYTICUS MENINGITIS IN AN INFANT

Treatment With Sulfonamides Orally With Recovery

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STAPHYLOCOCCIC meningitis, as has been well recognized probably even from antiquity,[1] is a serious illness sustaining a relatively low morbidity but a very high mortality. Holt,[2] in 1911, reporting 197 cases of proved meningitis seen in the Babies' Hospital, New York City, stated that "The common pyogenic organisms, streptococcus and staphylococcus, have been very infrequently found by me as the cause of meningitis. They were present in but ten cases. It is rather striking that six of the ten cases occurred in newly born children, and that in five the meningitis was secondary to spina bifida. Under such circumstances they are always fatal." Fothergill and Sweet,[3] in 1933, reported 705 cases of meningitis that they had seen over a twelve-year period (1921 to 1933) at the Infants' and Children's Hospitals, Boston. Fifteen cases (2 per cent) were due to the staphylococcus. Three cases were due to the *Staphylococcus albus* complicating hydrocephalus or chronic meningococcic meningitis. One of the patients recovered. Twelve cases were due to *Staphylococcus aureus;* all terminated fatally. Of 1,100 cases of meningitis occurring in infancy and childhood collected by Silverthorne[4] (Hospital for Sick Children, Toronto, Canada) over a period of twenty-two years (1919-1941) but twenty-five cases (2.3 per cent) were staphylococcic in etiology (two patients recovered).

Even up to very recent times, staphylococcic infection of the meninges has been regarded as being a hopeless disease. The first reported recovered cases were treated by spinal and cisternal drainage and by divers surgical procedures. Later, recoveries following the use of methenamine, methylrosaniline (gentian violet), bacteriophage therapy, staphylococcus vaccine, and staphylococcus antitoxin were made known.

In a comprehensive review of the subject of staphylococcic meningitis from the years 1893 to 1942, MacNeal and coauthors[5a] found that although first mention of cure from this disease was made in 1899 by Josias and Netter,[5b] who reported a patient who had *Staphylococcus aureus* meningitis, yet they were able to find only forty-eight reported recoveries in the world literature. In 1899, von Bergmann[5c] also reported recovery in a case of meningitis, the causative organism being the *Staph. albus.* Treatment consisted of repeated taps of a meningocele site which had become infected following operation. Poirer,[5d] in 1900, reported successful surgical treatment in a case of septic meningitis. Before operation a lumbar puncture revealed bloody fluid which yielded both the *Staph. aureus* and the *Staph. albus.* Some of the cases in which recovery from staphylococcic meningitis was reported were probably not true cases of the disease, but were, rather, localized infections of the meninges.

Benoit,[6] noting several clinical forms of this illness, differentiated between: (1) infection of the meninges following staphylococcic invasion of the blood stream; (2) meningitis arising from a focus of inflammation, from the ear, scalp, vertebrae; (3) meningitis following trauma, especially war wounds. His cautioning against spinal puncture in case of epidural infection because of the danger of transferring the infection into the subarachnoid space and thereby producing a meningitis, has been stressed repeatedly. Rosamund[7] reported such an occurrence in a female child 6 years of age. The patient recovered after laminectomy. Schless,[8] observing that some cases of *Staph. aureus* meningitis were of a localized nature while many were of a generalized more severe type, devised a similar classification. He divided the staphylococcic meningitides into four groups: (1) Localized abscess involving the meninges and caused by an extension of infection from adjacent tissue. Here surgery is of avail. (2) Meningitis occurring as the result of staphylococcic septicemia with generalized infection. The prognosis is fatal. (3) Meningitis of hematogenous origin secondary to staphylococcic infection in noncontiguous structures. Characteristic signs of frank meningitis are present with positive cultures of *Staph. aureus.* (4) Noncharacteristic meningitis (Lamb's case[9]; Table I). If cases of recovery from the diffuse type of staphylococcic meningitis only are listed, the number of recoveries from staphylococcic meningitis remains relatively few.

TABLE I. SUMMARY OF RECOVERED CASES OF STAPHYLOCOCCIC MENINGITIS IN INFANCY (BIRTH TO TWO YEARS)

YEAR	AUTHOR	ORGANISM	SPINAL FLUID CULTURE	BLOOD CULTURE	AGE	SEX	THERAPY
1928	Lamb[9]	*Staph. aureus*	+	-	Infant	F	Methylrosaniline 0.1 per cent. (intraventrically), spinal and cisternal drainage
1938	Block and Pacella[10]	*Staph. aureus*	Not mentioned	Not mentioned	17 days	M	Sulfanilamide (orally and intrathecally)
1940	Dietel and Kaiser[11]	*Staph. aureus*	+	Not mentioned	20 mo.	M	Sulfathiazole (by stomach tube)
1941	Donovan[12]	*Staph. aureus*	+	+	7 mo.	M	Sulfapyradine (orally), sulfathiazole (orally and intravenously)

Since the introduction of the sulfonamides and their proved efficacy against many pathogenic microorganisms, the outcome of treatment of this highly fatal malady is more hopeful. The attack against the purulent meningitides has been accelerated so that an increase in number of recoveries may be

expected to be added to the medical literature. The total number of reported cures from staphylococcic meningitis remains small, however, especially in the age group below 2 years (Table I).

In view of the recent advances in the treatment of meningitis with the use of the sulfonamides, we believe it is of value to record an additional case of recovery from staphylococcic meningitis following sulfonamide medication. The case recorded here occurred in the youngest patient yet reported recovering from meningitis caused by *Staphylococcus albus hemolyticus.*

REPORT OF CASE

History.—M. C., white female, aged 12 months, was seen on Dec. 8, 1943, because of an upper respiratory infection of one week's duration. The rectal temperature was 101° F.; pulse, 104; respiration, 22. The parents stated that the infant in the last two days had appeared to improve but on the evening of December 7 had jerked all night with fever. The past history was noncontributory. The birth, feeding, physical and mental developmental histories were irrelevant. Examination at that time revealed an acute tonsillitis, there being a few small discrete patches of whitish exudate on both tonsils. No free bleeding occurred after removal of some of the exudate. A throat culture was taken. In addition to the tonsillitis there was mild flushing of the eardrums. The chest was clear; the heart was essentially negative. The white blood count was 12,700 per cubic millimeter with 66 per cent polymorphonuclear leucocytes and 34 per cent lymphocytes. Sulfathiazole, ear drops, and a sedative were prescribed. The patient did not yet appear acutely ill. On December 11, the patient was seen again. At that time in spite of an improvement of the fever and in the condition of the throat, the infant appeared moderately ill. The culture of the throat was reported as revealing colonies of staphylococci. No abnormal neurological signs were evident. The anterior fontanel was soft and not bulging. The mother stated that the patient refused to take the sulfathiazole. Hospitalization was advised, but the infant was not taken to the hospital until the next day.

Physical Examination.—On admission to the hospital Dec. 12, 1943, the baby was acutely ill and the rectal temperature was 103° F. No coughing, vomiting, diarrhea, or convulsions had occurred. The throat was improved but still mildly inflamed, no exudate now being present on the tonsils. The eardrums were still mildly injected. The anterior fontanel now was tense and very slightly bulging. The pupils were slightly dilated and reacted to light. The heart and lungs were essentially negative. The abdomen was slightly distended; there was no enlargement of the liver or spleen. The deep reflexes were hyperactive. Both Kernig's and Brudzinski's tests were negative. Nuchal rigidity was absent.

Laboratory Data.—A spinal puncture was performed soon after admission and revealed cloudy fluid under increased pressure. The cell count was 952 cells per cubic millimeter, 88 per cent being polymorphonuclears and 12 per cent mononuclears. A smear of the centrifuged sediment revealed scattered small clumps of gram-positive cocci. The globulin was increased (2 plus) and the sugar content was within normal limits qualitatively. Two days later the culture revealed *Staph. albus hemolyticus.* A blood culture taken December 12, revealed *Staph. albus hemolyticus.* The white blood count was 19,700 per cubic millimeter, 56 per cent being polymorphonuclear leucocytes, 42 per cent lymphocytes, and 2 per cent monocytes. The blood contained 12.2 Gm. of hemoglobin per cubic centimeter. A urinalysis was negative. The blood Kahn reaction was negative. A roentgenogram of the chest revealed no abnormality of the heart or lungs. Additional laboratory examinations of red blood cells, hemoglobin, white blood cells and differential count, as well as urine, were made every few days (Fig. 1). *Bacteriology:* A gram-positive coccus which grew in clumps was isolated both from the cerebrospinal fluid and the blood. On blood agar plates hemolytic areas surrounded each small, glistening creamish colony. No yellow pigment was formed, even after transfer.

Clinical Course and Treatment (Fig. 1).—The patient's stay in the hospital extended over a period of twenty-five days. Before the reports of the spinal fluid and blood cultures were forthcoming, sulfadiazine, 0.2 Gm. (3 grains), was given orally every four hours for forty-eight hours for a total dosage of 2.38 Gm. (36 grains). When the cultures yielding *Staph. albus hemolyticus* were viewed, sulfadiazine therapy was changed to sulfathiazole and maintained in oral doses of 0.38 Gm. (6 grains) every three hours. This dosage was continued for four days when 0.38 Gm. (6 grains) was administered every four hours after the infant appeared to be improving. As satisfactory progress continued, the sulfathiazole dosage

was gradually decreased. On two occasions the intake of the drug was augmented when there was an increase in the fever and symptoms following a reduction in dosage of the medication. Only two spinal punctures were performed during the entire illness. The first we have already mentioned. The second spinal tap on the seventh hospital day revealed a clear fluid under no increase of pressure; 80 cells were present, 50 per cent polymorphonuclears and 50 per cent mononuclears. The culture revealed no growth of organisms. A blood sample taken the same date was still sterile after ten days' culture.

On the patient's third day in the hospital opisthotonos and nuchal rigidity made their appearance and continued for five days. The anterior fontanel, bulging on admission, became soft on the seventh hospital day. By the eighth day clinical improvement was evident and continued until discharge.

Adjuvant therapy consisted of parenteral fluids of 2.5 per cent glucose, physiologic saline, and blood transfusions.

Follow-up.—The patient was seen four weeks and again ten weeks after discharge from the hospital, because of roseola infantum and varicella, respectively. No residual effects of the meningitis were present at either time. The infant had made a complete recovery from the meningitis.

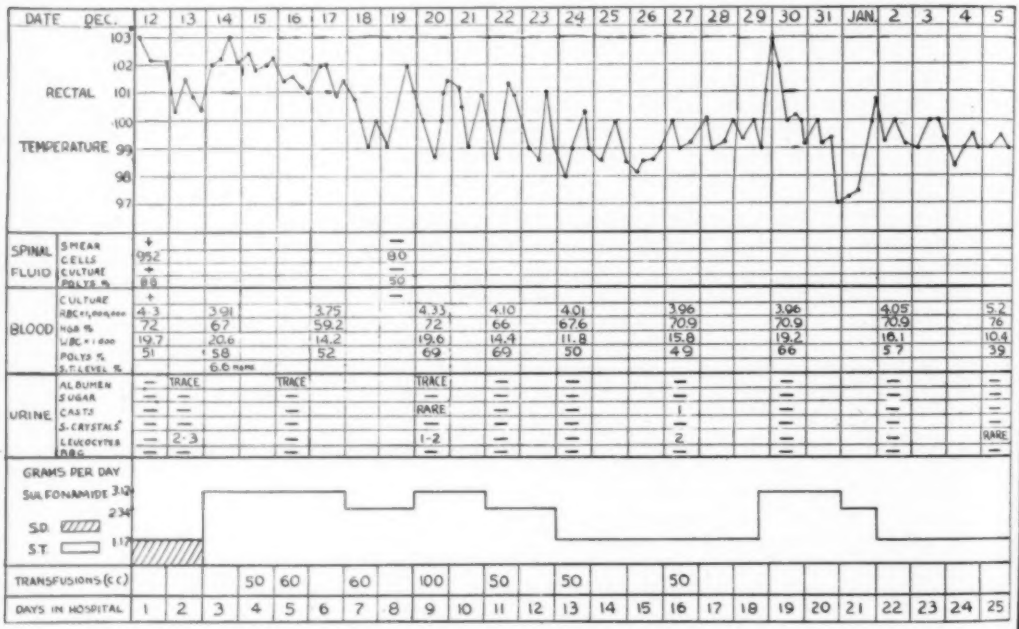

Fig. 1.—Clinical course of *Staph. albus hemolyticus* meningitis in a 12-month-old infant. *S.*, sulfonamide; *S.D.*, sulfadiazine; *S.T.*, sulfathiazole.

COMMENT

Although we could not discover any pertinent literature substantiating our findings we were impressed by the fact that *Staph. albus* meningitis may be less severe than meningitis due to *Staph. aureus*, no differences in the type of meningitis withstanding.

Fothergill and Sweet[3] in a short discussion of their cases of *Staph. albus* meningitis stated that in each instance the infection was relatively benign and continued for a long period of time. One of the three patients recovered from the infection. No mention is made of therapy. Salvini[13] cited a case of *Staph. albus* meningitis in an adult aged 33 years who recovered with thecal drainage and intravenous injections of methenamine. He recovered the organism from

the spinal fluid and the blood. Cocci were present in the spinal fluid sediment. Infected tonsils were believed to be the focus of infection.

Before the advent of the sulfonamides as chemotherapeutic agents, successful treatment of staphylococcic meningitis was uncertain, and survival, therefore, was of most unusual interest. Surgical procedures were of use where the infection was localized. In rare cases of even the apparent frank type of meningitis in the young patient, thecal drainage alone without any specific medication resulted in a cure. A case in point is that of Jackson[14] who reported in 1937 the recovery of a child aged 2½ years from *Staph. aureus* meningitis. The organism was recovered from both the spinal fluid and the blood. Treatment was by cisternal punctures to relieve the increase in intracranial pressure. Blood transfusions and parenteral fluids were given. The author believed that the favorable outcome was due to the fact that the infection was self-limited. The blood transfusions, however, may have been the important curative factor.

Following the introduction of the sulfonamides, the treatment of septic meningitis has taken a radical change, having resolved itself practically to initial spinal puncture for determining diagnosis and then to the employment of a sulfonamide (sulfathiazole, sulfadiazine, or sulfapyrazine) either orally or parenterally. Some clinicians believe it not necessary to drain the spinal fluid frequently. Silverthorne,[4] however, emphasizes the importance of doing more than the diagnostic lumbar puncture. He stresses the importance of doing frequent cell count, culture, and sulfonamide levels of the cerebrospinal fluid in accurately charting the course of the disease. Furthermore, intrathecal use of the sulfonamide derivative may be no more efficacious than if given by mouth or intravenously. Donovan[12] gave large doses of sulfathiazole both by mouth and by vein. A total sulfathiazole level of 9.5 mg. per cent in the spinal fluid dropped to 1.9 mg. per cent in forty-eight hours despite continued therapy. The spinal fluid level of sulfathiazole after seventy-two hours of medication with this sulfonamide never was more than 3.7 mg. per cent, yet progress was satisfactory.

Treatment of staphylococcic meningitis with successful outcome has been reported by Stout,[15] Schless,[8] Dunlap,[16] MacNeal,[17] and MacNeal and Foster[18] following the use of staphylococcus bacteriophage. In a review of ten years of bacteriophage service for various staphylococcic infections, MacNeal, Frisbee, and Blevins[19] cited five hithertofore unreported recoveries from diffuse cerebrospinal staphylococcic leptomeningitis, one from local cerebral meningitis, and one from local cervical pachymeningitis for which they supplied staphylococcic bacteriophage. They advocate the skillful use of bacteriophage, but also advise the use of a sulfonamide, especially sulfathiazole or sulfapyradine, along with the bacteriophage in treatment. The bacteriophage may be given by intravenous or intrathecal injection and should be continued for three months after recovery to prevent occurrence of any latent sequelae. The use of an antitoxic serum also is recommended in the first week. The authors believe, however, that the bacteriophage alone, adequately used, will result in the recovery of the most severe type of this disease.

The intravenous, intramuscular, and intrathecal use of penicillin has been recommended in the treatment of staphylococcic meningitis. Pilcher[20] states that intravenous penicillin was ineffective in experimental (dog) staphylococcic meningitis but intrathecal penicillin therapy was markedly beneficial. Although the use of intrathecal penicillin is advocated in the therapy of staphylococcic meningitis, successful treatment may result after the use of only intravenous or intramuscular injections. Price and Hodges[21] reported seven recoveries from

meningitis (one of staphylococcic etiology) in which cure followed systemic penicilliin therapy by intramuscular and intravenous routes. The medication was given continuously. Penicillin, while effective against *Staph. aureus* is not equally potent, however, against many strains of *Staph. albus*, and therefore its use in staphylococcic meningitis is limited.

The synergistic action of penicillin and the sulfonamide compounds, especially sulfathiazole, has been demonstrated.[22] Their combined use against staphylococcic meningitis holds great promise in increasing the recovery rate of this highly fatal malady.

Thus, in the armamentarium against staphylococcic meningitis, three types of therapy are available: specific bacteriophage, sulfonamide compounds, and penicillin. These may be used alone, or better yet, in combination. Early diagnosis and adequate continuous medication, however, are still the essential features in successful treatment.

In the employment of adjuvant therapy, transfusions of blood should be considered of prime importance not only in counteracting the anemia that occurs with the extended use of sulfonamides, but also because blood may supply a high titer of specific antibodies.

SUMMARY

A case of complete recovery from staphylococcic meningitis in a female infant 12 months of age is reported. The causative organism, *Staph. albus hemolyticus*, was isolated from both blood and spinal fluid. The source of infection was probably in the upper respiratory tract. Recovery occurred after the oral use of sulfadiazine and sulfathiazole. Adjuvant therapy consisted of blood transfusions and parenteral fluids.

REFERENCES

1. MacNeal, W. J., Frisbee, F. C., and Blevins, A.: Arch. Otolaryng. **37**: 199, 1943.
2. Holt, L. E.: Am. J. Dis. Child. **1**: 26, 1911.
3. Fothergill, L. D., and Sweet, L. K.: J. PEDIAT. **2**: 696, 1933.
4. Silverthorne, N.: Canad. M. A. J. **48**: 218, 1943.
5. (a) MacNeal, W. J., Frisbee, F. C., and Blevins, A.: Arch. Otolaryng. **37**: 349, 1943.
   (b) Josias and Netter: Cited by MacNeal et al.[5a]
   (c) Von Bergmann: ibid.
   (d) Poirer: ibid.
6. Benoit, M.: Thesis, Toulouse, Henri Cléder, 1929.
7. Rosamund, E.: J. PEDIAT. **1**: 230, 1932.
8. Schless, R. A.: Am. J. Dis. Child. **44**: 813, 1932.
9. Lamb, F. H.: Arch. Pediat. **45**: 306, 1928.
10. Block, H., and Pacella, B. L.: J. A. M. A. **110**: 508, 1938.
11. Dietel, F. W., and Kaiser, A. D.: J. A. M. A. **115**: 601, 1940.
12. Donovan, T. J.: J. PEDIAT. **18**: 518, 1941.
13. Salvini, C.: Pensiero med. **17**: 263, 1928.
14. Jackson, R. L.: J. PEDIAT. **11**: 518, 1937.
15. Stout, B. F.: Texas State J. Med. **29**: 205, 1933.
16. Dunlap, J. E.: J. A. M. A. **104**: 1594, 1935.
17. MacNeal, W. J.: New York State J. Med. **41**: 1531, 1941.
18. MacNeal, P. S., and Foster, D. B.: Am. J. M. Sc. **202**: 874, 1941.
19. MacNeal, W. J., Frisbee, F. C., and Blevins, A.: Arch. Otolaryng. **37**: 507, 1943.
20. Pilcher, C.: Ann. Surg. **119**: 509, 1944.
21. Price, A. H., and Hodges, J. H.: New York State J. Med. **44**: 2012, 1944.
22. Bigger, J. W.: Lancet **2**: 142, 1944.

STREPTOCOCCAL VIRIDANS MENINGITIS FOLLOWED BY PNEUMOCOCCAL MENINGITIS IN THE SAME PATIENT WITH RECOVERY

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STREPTOCOCCAL viridans meningitis is a relatively rare disease and there have been but few reports of such cases in the literature. It appears that the vast majority of such cases are secondary to subacute bacterial endocarditis and are uniformly fatal. However, recoveries have been reported in those instances where the disease was either primary, as far as could be determined, or secondary to some focus in the body other than the valves of the heart. Gray,[1] reviewing the literature from 1900 to 1935, reported five recoveries. Treatment used varied considerably but included such methods as repeated lumbar taps, blood transfusions, and removal of discernible foci of infection. Trachsler, Frauenberger, Wagner, and Mitchell[2] in 1937 added four more recoveries from the literature in which nonspecific therapy was used. In some of these nine cases the foci of infection are unknown, while in others scalp laceration, otitis media, and sinusitis are listed as the primary sites of the disease.

The advent of the sulfonamides saw specific therapy being used for the first time. Mitchell, Bower, and Hamilton[3] reported six patients with streptococcal viridans meningitis treated with the sulfonamide drugs. Two of these received sulfapyridine and deep roentgen ray therapy before a cure was efpeated lumbar taps, blood transfusions, and removal of discernible foci of in- In 1941 Blumberg and Zisserman[4] added another case of a cure of primary streptococcal viridans meningitis with sulfapyridine. A case of streptococcal viridans sepsis neonatorum with meningitis in a 5-day-old infant cured with sulfapyridine in which the initial site of the infection appeared to be the umbilicus was reported by Greengard, Raycroft, and Motell.[5]

Rantz[6] in 1942, considering the problem of streptococcal meningitis, made some interesting observations concerning the frequency of the occurrence, mortality, and therapy. He states that 17 per cent of all bacterial meningitis are caused by streptococci, and of these only 20 per cent are nonhemolytic or form green pigment on blood agar. Without effective therapy the mortality rate for all types of streptococcal meningitis is 95 per cent, while with the sulfonamides the mortality rate is reduced to 20 per cent. He claims that sulfapyridine is effective against streptococcal viridans meningitis but sulfanilamide is not.

With the discovery and clinical application of penicillin, a new and efficacious agent was added to our armamentarium in the treatment of streptococcal viridans meningitis. Although few cases of its use are mentioned as yet, those that are seem to indicate that it is the most valuable means so far in combating this disease. Fleming[7] reported a patient who failed to respond to a course of sulfapyridine and sulfathiazole, but who responded promptly to penicillin given intrathecally and intramuscularly. In vitro studies showed the organism to be resistant to the sulfonamide drugs but susceptible to penicillin. In 1944 Rosenberg and Arling[8] added two more cures of streptococcal viridans meningitis in which penicillin was used.

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Pneumococcal meningitis is not so rare a disease as is streptococcal meningitis. Nevertheless, until recently, recovery has been a rare event indeed. We will not review the literature on pneumococcal meningitis as extensively as we did in streptococcal meningitis, as the facts are more generally known in the former disease. But it may be mentioned that before the utilization of specific therapy, the mortality rate in pneumococcal meningitis was over 99 per cent. When the sulfonamides came into use along with type specific rabbit serum, various reports had mortality figures ranging from 30 per cent to 80 per cent.

Penicillin has been used alone in the treatment of pneumococcal meningitis with very questionable results. Waring and Smith[9] treated twelve patients using penicillin and sulfonamides concurrently and obtained eleven cures. The one fatality occurred only ten hours after admission. In several of their cases, penicillin was used alone at first to no avail. The addition of sulfonamide therapy brought about rapid improvement and ultimate cure. These authors cited a report to the National Research Council in which twenty-one patients were treated with penicillin alone in which there were only seven cures. The general opinion seems to be today that combined penicillin and sulfonamide therapy is the treatment of choice in pneumococcal meningitis.

We wish to report a case in which the patient had streptococcal viridans meningitis and was cured by combined sulfadiazine and penicillin therapy. This same patient, approximately three months after the initial attack, developed pneumococcal meningitis and again a cure was effected by sulfadiazine and penicillin used concomitantly.

CASE REPORT

T. L., a 9-year-old white girl, was admitted to the Kings County Hospital, Aug. 11, 1944, because of headache, fever, and vomiting. Five days before admission she began to complain of severe frontal headache. Shortly after her headache began, she vomited. These symptoms continued for three days and a doctor was called who gave her some pills which afforded only slight relief. On the day of admission her headache was more severe, her vomiting persisted, and she felt feverish. For this reason her physician suggested that she be brought to the hospital.

Physical examination upon admission revealed a thin, pale, white girl who appeared acutely ill. She was lethargic and not well aware of her surroundings. The skin was dry and warm. The temperature was 101.6° F. The pulse was 88, and the respirations were 20. The ears were clear, and the pharynx was slightly injected. Oral hygiene was poor, several carious teeth being noted. Examination of the lungs, heart, and abdomen was negative. There was no weakness of the extremities, but some tenderness of the calf muscles was noted. There was marked nuchal rigidity. Kernig and Brudzinski reflexes were absent. Deep tendon reflexes were present and appeared to be normal. The abdominal reflexes were equal and active bilaterally. There was no Babinski reflex.

The impression at this time was that the child had either meningitis or poliomyelitis. A lumbar puncture was performed for diagnostic purposes. A hazy fluid under increased pressure was obtained. The cell count was approximately 1,000 cm. with about 90 per cent polymorphonuclear leucocytes and 10 per cent lymphocytes. The Pandy test was positive. No organisms were seen on the initial smear performed by the intern. There were 11 Gm. of hemoglobin and the red count was 3,420,000. The white blood count was 7,800. Forty-four per cent of the cells were polymorphonuclear leucocytes; 54 per cent, lymphocytes; and 2 per cent, monocytes. The urine was normal.

Although the evidence at this time was not conclusive, it was felt that there was a strong likelihood that the child was suffering from a bacterial meningitis. Therefore treatment was started with this in mind. She was given an initial dose of 3 Gm. (60 c.c.) of 5 per cent sodium sulfadiazine and this was followed by oral sulfadiazine, 1 Gm. every 4 hours. After the initial intravenous dose of chemotherapy an infusion of 2,000 c.c. of one-half glucose and saline and one-half glucose and water was given.

The following morning the patient appeared slightly improved. Her temperature was 100.8° F. at this time. There was still marked nuchal rigidity, but there were no pathologic reflexes present. A report from the laboratory on the spinal fluid revealed that the smear showed many gram-positive cocci and a few decolorized cocci occurring in short chains. The protein was 49 mg. per cent and the sugar was less than 10 mg. per cent. It was felt at this time that the organism was either a streptococcus or less likely a pneumococcus. That afternoon the patient became more lethargic and took fluids poorly. For this reason she was given another 2,000 c.c. of fluids intravenously. On the third hospital day the patient still took fluids poorly and parenteral fluids had to be continued. That evening her temperature spiked to 103° F. and she appeared acutely ill and toxic. Aspirin and an alcohol rub were given with good results. The following morning the child appeared markedly improved. She took fluids well and appeared brighter than at any other time since admission to the hospital. The culture of the spinal fluid obtained upon admission showed the organism to be *Streptococcus viridans*. Since she showed some improvement at this time, it was decided to continue with sulfonamide therapy. A second spinal tap revealed a hazy fluid with increased cell count and positive Pandy. Subsequent report from the laboratory showed this fluid to have *Str. viridans* by culture. The protein was elevated markedly and the sugar was below 10 mg. per cent.

The patient ran a low-grade fever on the fifth hospital day and signs of meningeal irritation appeared to be decreasing. However, on the evening of the sixth day the temperature rose to 104° F. and she appeared extremely ill. She vomited sulfadiazine and took fluids poorly. There was marked nuchal rigidity. Daily sulfadiazine levels up to this time revealed levels between 9 and 12 mg. per cent. Since there was obviously no response to sulfadiazine, it was decided to start penicillin. She was given 20,000 units of penicillin intrathecally dissolved in 20 c.c. of sterile water and 20,000 units intramuscularly. A routine was instituted whereby the patient was to be given 20,000 units intrathecally daily and 10,000 units intramuscularly every three hours. Sulfadiazine was continued.

On the eighth hospital day her temperature became normal and remained normal for the remainder of her stay in the hospital. This was thirty-six hours after penicillin therapy was started. The spinal fluid culture was sterile twenty-four hours after penicillin had been initiated and also remained sterile thereafter. At this time she had no meningeal signs and appeared markedly improved. Although the spinal fluid was sterile at this time, the cell count was still elevated, the protein high, and the sugar low. It was felt that therapy should be continued as outlined until these constituents of the spinal fluid approached normal.

Sulfadiazine was discontinued on the eleventh day, the patient having received a total of 63 Gm. After this medication was stopped there was no further rise in temperature or recurrence of symptoms. Treatment with penicillin was continued intramuscularly and intrathecally as outlined until the patient's fourteenth hospital day. The spinal fluid had approached normal for the preceding forty-eight hours. The patient during her course of therapy had received penicillin for nine days and had received a total of 910,000 units intrathecally and intramuscularly. After all treatment was terminated, the patient remained perfectly asymptomatic.

During the patient's stay in the hospital an effort was made to find a possible focus for this infection. Examination of the ears, nose, throat, and sinuses by members of the otolaryngology department proved negative. The possibility of this being secondary to a subacute bacterial endocarditis was also considered. Careful clinical examination of the heart by members of the staff revealed the heart action to be quiet. There were no murmurs except a short, blowing systolic at the pulmonic area. No petechiae were noted. The eyegrounds were normal. Blood cultures repeated at frequent times were always sterile. No abnormalities were found in the urine. The culture of the urine was sterile. Laboratory study for any evidence of cardiac pathology which might predispose to subacute bacterial endocarditis was also negative. This included x-ray, electrocardiogram, vital capacity, and sedimentation rate.

Because of the child's poor state of oral hygiene, members of the dental staff were called in. It was felt that there was a strong possibility that some connection existed between the state of her teeth and her meningitis. Their clinical examination revealed the presence of two extremely carious, lower, first molar teeth with pulp exposures. X-ray examination of the teeth showed that at the apex of the lower right there was a chronic, alveolar abscess at each of the two roots. At the apex of the lower left there was a chronic, alveolar abscess at the apex of one root. Smear and culture from these sites

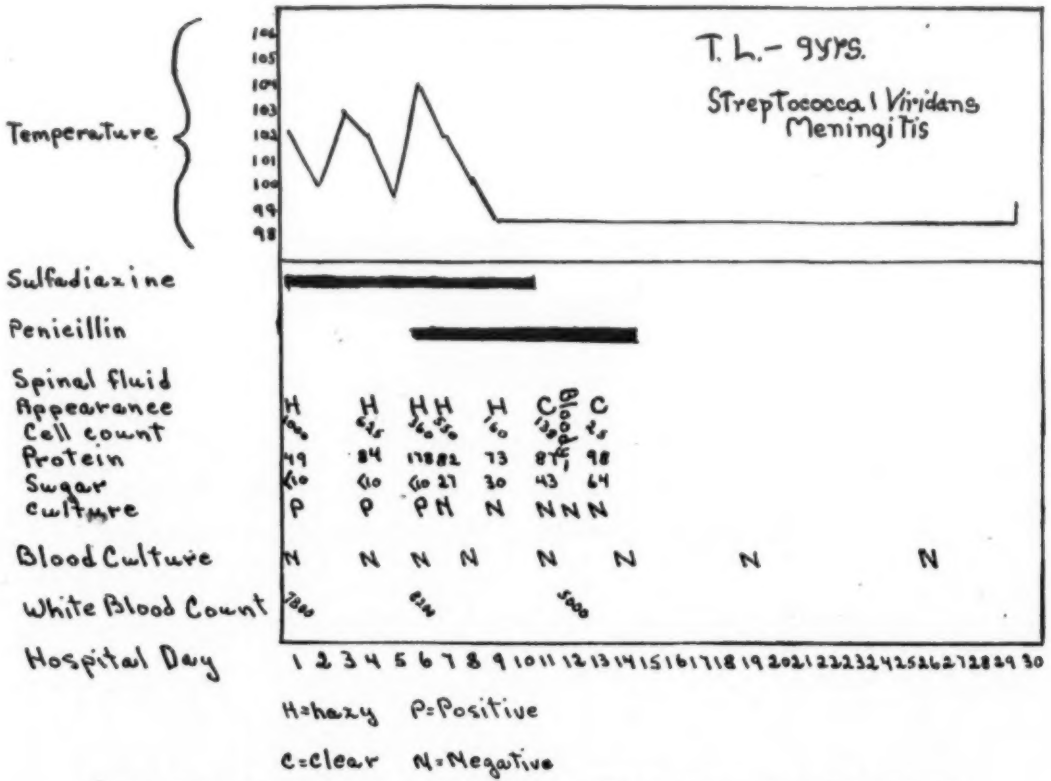

Chart 1.—Patient's clinical course in hospital during episode of streptococcal viridans meningitis.

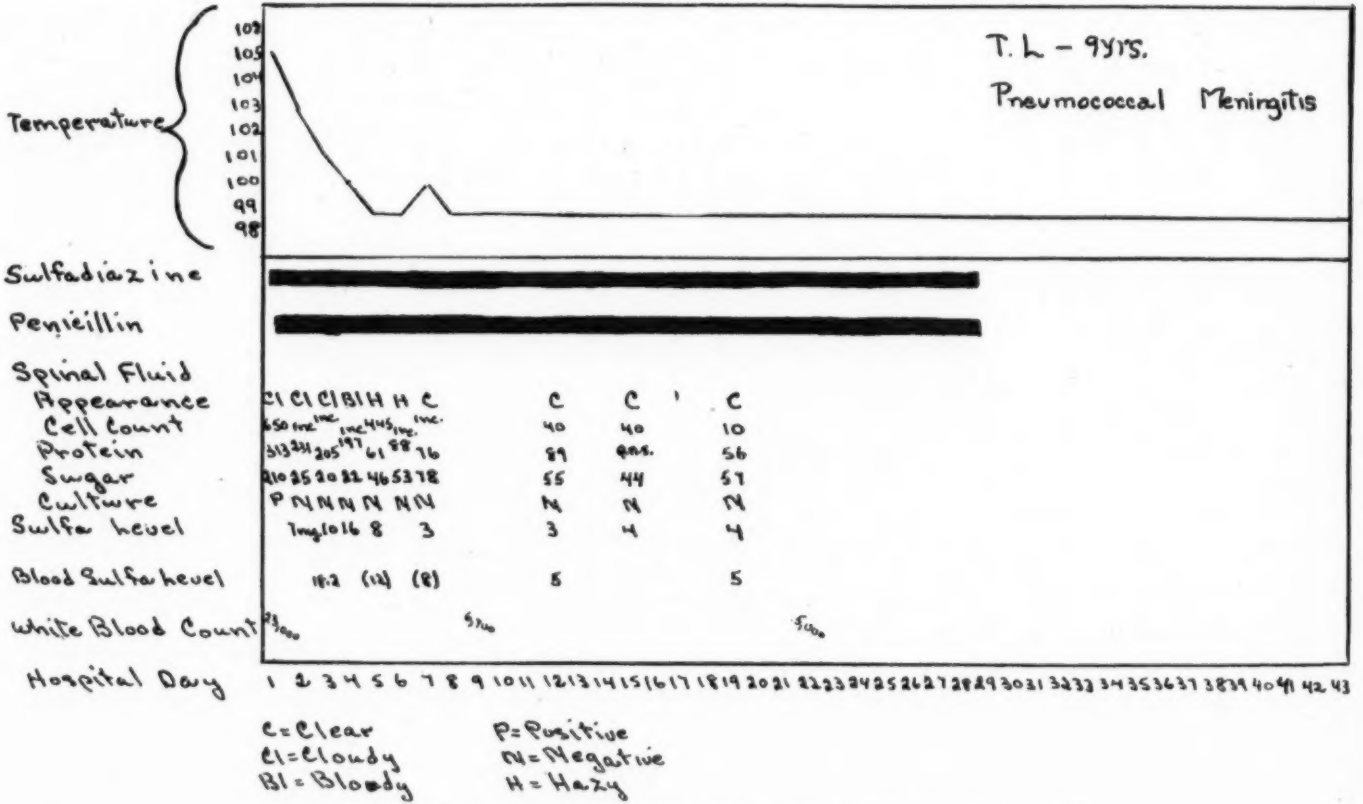

Chart 2.—Patient's clinical course in hospital during episode of pneumococcal meningitis.

revealed the presence of *Str. viridans* in large numbers. No methods were available at the time to show that these organisms were the same in type as those found in the spinal fluid of the patient.

The patient was discharged on September 6 after twenty-nine days of hospitalization. Arrangements were made for her to be readmitted in a short time for extraction of the infected teeth under adequate chemotherapy, since they were probably the focus of the infection.

The patient returned to the pediatric ward of Kings County Hospital on Oct. 6, 1944, for dental extraction. Forty-five minutes before the extractions were performed she was given 20,000 units of penicillin intramuscularly. The same dose was repeated immediately upon return from the dental clinic to the ward which was about fifteen minutes after the extractions. At the moment of extraction cultures were taken from the exposed sockets for a bacteriologic study.

The patient remained afebrile and asymptomatic after the procedure. Her blood cultures were sterile. After ten days of uneventful hospital stay she was discharged on Oct. 19, 1944.

After discharge from the hospital the patient remained asymptomatic and returned to normal activities. During the day of November 26, about five weeks after her second hospital admission, she complained of a pain in her right ear. However, she did not appear to be very ill and she went to bed that night in apparent good health. At approximately 2 A.M. the following morning she awoke with a severe headache. She was given some water, but vomited this about twenty minutes later. During the morning her condition became progressively worse. She became feverish, her headache increased in severity, and she vomited everything ingested. At about 10 A.M. her mother phoned the Kings County Hospital and was told to bring the child in immediately.

On admission to the hospital about four hours later, the child was seen to be acutely ill. She was delirious and lay tossing and turning about without appearing to recognize anyone. Her rectal temperature was 105° F., her pulse was 108, and her respirations were 40. There was marked nuchal rigidity. Examination of the ears revealed that the right drum was bulging and red, and the landmarks were obliterated. The left ear was normal, the pharynx and the tonsils were markedly inflamed. Examination of the lungs and heart revealed nothing of note. The deep tendon reflexes were unimpaired. The Kernig and Brudzinski reflexes were both present. There was no Babinski reflex.

The impression at the time of this admission was that the child had a recurrence of streptococcal viridans meningitis. In view of the preceding history of this case, it was decided to start therapy immediately with sulfadiazine and with penicillin both intramuscularly and intrathecally. When the initial spinal tap was performed, a cloudy fluid under considerably increased pressure was obtained. About 10 c.c. of this fluid were withdrawn and 20,000 units of penicillin dissolved in 10 c.c. of normal saline injected into the spinal canal. Examination of the spinal fluid revealed about 650 cells per cubic millimeter with about 90 per cent polymorphonuclear leucocytes. The Pandy test was markedly positive. Smear of the fluid revealed an enormous number of gram-positive and decolorized cocci in pairs and short chains which resembled either pneumococci or streptococci. A blood count was done on admission. There were 11.5 Gm. of hemoglobin and the red count was 3,250,000. The white blood count was 23,000, and there were 86 per cent polymorphonuclear leucocytes and 14 per cent lymphocytes. The urine examination revealed nothing of note.

After the initial spinal tap during which the first dose of intrathecal penicillin was given, the patient was given 20,000 units of penicillin intramuscularly. This therapy was repeated every three hours night and day. An intravenous infusion was started then of alternating 5 per cent glucose and saline and Hartmann's solution. This infusion was continuous for the first twenty-four hours of hospitalization. Three grams of sodium sulfadiazine were given through the infusion tubing shortly after admission, and 1-gram doses repeated intravenously every four hours thereafter as long as the infusion was kept going.

On the night of admission the patient's temperature went up to 105.8° F., and her pulse rate rose to 140 and appeared weak and thready. At this time her condition appeared very poor. However, the following morning her temperature had dropped to 102.4° F. and she appeared somewhat improved. She was not as restless and not nearly so disoriented as she was upon admission. Signs of meningeal irritation were still present, however. Report on the spinal fluid at this time from the laboratory revealed that the infecting organism was pneumococcus type XII. The protein was 313 mg. per cent and the sugar was less than 10 mg. per cent. Blood culture on admission also revealed pneumococcus type XII.

Since the patient appeared to be improved, intravenous therapy was discontinued and both fluids and sulfadiazine were given by mouth. Penicillin was given intrathecally on the second hospital day as it had been given on the first. It had been decided previously to give penicillin intrathecally daily until the spinal fluid findings had returned to normal.

On the third hospital day the patient's temperature had dropped to 100.8° F. and further clinical improvement was noted. Report on the spinal fluid withdrawn the day previously revealed that although cloudy, both smear and culture were negative. The spinal fluid specimens remained sterile for the remainder of her hospital stay. Similarly, all subsequent blood cultures were sterile.

Her temperature was normal on the fourth hospital day. Marked improvement in her condition could be seen. Nuchal rigidity was still present but was markedly diminished. The signs of inflammation in the right eardrum, tonsils, and pharynx were almost completely resolved. On this day a supportive transfusion of 250 c.c. of blood was given.

On the fifth hospital day many sulfonamide crystals and some red blood cells were noted in the urine. Fluid intake and output had been inadequate on the previous day and it was felt that this had to be corrected. Sulfadiazine, therefore, was eliminated for two doses and then reinstated at dosages of 0.5 Gm. every four hours. Fluids were forced for the next forty-eight hours by means of a stomach tube. The urinary findings cleared within twenty-four hours.

The remainder of the child's stay in the hospital was uneventful. Penicillin was given intrathecally daily for the first seven hospital days. The spinal fluid sugar level which was used as a guide for intrathecal therapy increased from less than 10 mg. per cent on admission to a normal level of 53 mg. per cent on the sixth hospital day and remained normal thereafter. On the sixth hospital day the intramuscular penicillin dosage was reduced to 10,000 units every three hours. Penicillin was continued along with sulfadiazine through the twenty-eighth hospital day. At this time medication was discontinued. During the period of this hospitalization, laboratory studies revealed that the penicillin resistance of this organism infecting the patient was 0.0039 Florey units. The penicillin levels on the body fluids (spinal fluid and blood) reached levels as high as 0.31 Florey units per cubic centimeter. It can be seen, therefore, that the pneumococcus causing this infection was susceptible to penicillin therapy. Sulfonamide levels taken on both blood and spinal fluid appeared to be adequate.

The patient spent two weeks convalescing on the ward of the hospital. During this time careful clinical observation failed to reveal any signs of recurrence of symptoms. She was discharged on the forty-third hospital day with no sequelae and in apparent good health.

COMMENT

From past experience it is known that the sulfonamides are not very effective against *Str. viridans*. Although many successes are reported in their use against this organism, the results are not as remarkable as when they are used against *Streptococcus hemolyticus*. In the case of streptococcal viridans meningitis reported here, we see dramatic clinical improvement in the patient following the addition of penicillin which was not seen with sulfadiazine. During the period of our patient's first hospital admission, sensitivity tests against sulfadiazine and penicillin were performed on the streptococcus which had caused the meningitis. It was found that growth was inhibited in vitro by a concentration of 10 mg. per cent of sulfadiazine but not by 5 mg. per cent. Growth was inhibited by penicillin in a concentration of 0.05 units per cubic centimeter but not by 0.025 units per cubic centimeter. (The "sensitive" hemolytic streptococcus used as control was inhibited by 0.01 units per cubic centimeter.) Blood levels of sulfadiazine exceeding 10 mg. per cent were reached in our patient. Similarly, penicillin levels exceeding 0.05 units per cubic centimeter were attained. Therefore from the laboratory findings one would expect that perhaps either sulfadiazine or penicillin were equally effective. However, the rapid improvement in our patient, following the addi-

tion of penicillin, makes us believe that this agent was the most important factor in her recovery. Of course it must be mentioned that sulfadiazine was continued along with penicillin and this may have contributed to the cure.

We felt that the focus of infection for our patient's streptococcal meningitis was her diseased teeth. In order to prevent a possible recurrence it was decided to remove these teeth. It is known that a transient bacteremia exists at the time of dental extraction. Prophylactic chemotherapy is a standard procedure when teeth are extracted in a rheumatic patient, the rationale being to prevent infection of the damaged valves by *Str. viridans,* the organism which usually enters the blood stream. It was felt that in our patient the meninges were a *locus minoris resistentiæ* and thus comparable to the damaged valves of the rheumatic heart. Therefore, when the presumed focus of infection was removed it seemed logical to maintain a sterile blood stream and thus prevent a reinfection of the meninges. Since it seemed to us that the *Str. viridans* that had caused our patient's meningitis was susceptible to penicillin and relatively refractory to sulfadiazine, the former agent was used as prophylaxis during the dental extraction rather than the latter.

As mentioned in the case report injections of penicillin were given forty-five minutes before, and fifteen minutes after the extraction of the teeth. Previous studies had indicated that penicillin injected intramuscularly reached its highest level thirty minutes later and disappeared from the blood stream in one hour and one-half. It was felt that by our procedure an optimum high blood level of penicillin would be reached at the time the teeth were extracted, at which time the chance for a bacteremia to occur was highest.

The question as to why our patient developed two attacks of meningitis with different organisms in such a short space of time must remain a matter of speculation. It is entirely conceivable, however, that her first infection lowered the resistance of the meninges in some way so as to render them susceptible to infection again. The patient at a later date developed a pneumococcal infection of her ear, pharynx, and tonsils, and a bacteremia resulted. The meninges being "damaged" or "susceptible" were thus readily infected again, and a definite pneumococcal meningitis resulted. Of course we cannot offer proof for this concept, but we merely offer it as a possible explanation for a very rare occurrence.

SUMMARY

1. A case is presented in which a patient had streptococcal viridans meningitis and was cured by combined sulfadiazine and penicillin therapy. Three months later the same patient developed pneumococcal meningitis and was again cured by the same therapy.

2. For the streptococcal meningitis, sulfadiazine was used at first with equivocal results. Penicillin was added and recovery occurred promptly. For the second infection both forms of therapy were used at the onset. Penicillin was used both intramuscularly and intraspinally.

3. The focus of infection for the streptococcal viridans meningitis was felt to be several diseased teeth. These were removed with penicillin being given prophylactically. The foci of infection for the pneumococcus meningitis were the right ear, pharynx, and tonsils.

4. Mention is made of the possibility of the meninges being made more susceptible to infection by the first attack.

REFERENCES

1. Gray, H. J.: J. A. M. A. 105: 92, 1935.
2. Trachsler, W. H., Frauenberger, G. S., Wagner, C., and Mitchell, A. G.: J. Pediat. 11: 249, 1937.
3. Mitchell, W. J., Bower, A. G., Hamilton, P. M.: Am. J. M. Sc. 200: 75, 1940.
4. Blumberg, Nathan, and Zisserman, Louis: M. Rec. 154: 349, 1941.
5. Greengard, J., Raycroft, W. B., Motell, W. G.: Arch. Pediat. 57: 770, 1940.
6. Rantz, L. A.: Ann. Int. Med. 16: 716, 1942.
7. Fleming, A.: Lancet 2: 434, 1943.
8. Rosenberg, D. H., and Arling, P. A.: U. S. Nav. M. Bull. 43: 281, 1944.
9. Waring, A. J., and Smith, M. H.: J. A. M. A. 126: 7, 1944.

THE WATERHOUSE-FRIDERICHSEN SYNDROME

A Report of Eight Cases at The Children's Hospital, Washington, D. C.

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AMONG those maladies tending toward more widespread recognition in diagnostic circles is that clinical-pathologic entity known as the Waterhouse-Friderichsen syndrome. Although much discussion has arisen as to the proper application of this term, present opinion would reserve its use for those cases in which there is a fairly constant group of clinical signs and symptoms typical of a fulminating septicemia (sudden onset, hyperpyrexia, purpura, cyanosis and shock) associated with a definite pathological picture embodying adrenal hemorrhage.

History.—Earliest report of this condition, according to Monfort and Mehrling,[21] occurred in 1894 when Völeker described fulminating purpura with bilateral adrenal hemorrhage. Next account of this disorder and an attempt at its explanation was made by Blaher and Bailey in 1901[4] who believed that a factor of blood poisoning should be considered. But Little,[18] in the same year, noted that bacteriology was negative in his series of cases. In 1911 Waterhouse[29] presented a similar series of cases with which he associated a distinct clinical picture. Friderichsen[9] in 1918 summarized the literature, but it was not until 1933 that the designation of Waterhouse-Friderichsen syndrome was attached to this disease by Glanzmann.[10] In a recent summary,[12] only 125 cases have been reported, the majority of these being in foreign journals. Of these, twenty-nine were cited since 1941. Lindsay, Rice, Selinger, and Robins[17] reported a series of seven cases with a review of the literature in 1941.

Etiology.—The causative agent for this syndrome remained uncertain for many years. Various organisms, including the pneumococcus, *Hemophilus influenzae*, diphtheria bacillus, streptococcus, and meningococcus were postulated as the etiological agent. However, careful bacteriologic studies in more recent times have shown the condition to be almost exclusively the result of fulminating meningococcemia. Thus, Thomas[27] reported a series of twenty-six patients dying as a result of meningococcemia before typical meningitic symptoms occurred; of twenty-three autopsies of this series, bilateral adrenal hemorrhage was reported in seventeen of the cases. Only one other organism, *Neisseria catarrhalis*, was found. In February, 1944, Thomas[28] again reported bilateral adrenal

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hemorrhage in twenty autopsy examinations of forty-nine cases expiring from meningococcal septicemia. Banks and McCartney[2] distinguish all fulminating meningococcic infections into typical encephalitic type of meningitis and the Waterhouse-Friderichsen syndrome.

There is no restricting age incidence although the vast majority of cases have occurred in children (90 per cent in patients 9 years and under; 70 per cent in children under 2 years). Martland[20] reported in his series a case occurring in a 50-year-old male. Holley[13] cited the case of an elderly white male of 70 years. The age incidence in the series now being reported ranges from 26 days to 11 years.

Symptomatology and Course of the Disease.—The patient is typically described as being in perfect health until the onset. In classical cases, the child awakens from sleep with a cry. He may be seen within two to three hours by a physician during which time hyperpyrexia, marked malaise, headache, vomiting, and abdominal pain usually may be present. First characteristic feature which usually prompts hospitalization is the accompanying cyanosis of the lips and nailbeds; closely following this the purpuric manifestations occur. These show themselves as hemorrhagic areas usually beginning on the limbs, trunk, and mucous membranes as tiny isolated points which rapidly enlarge and coalesce. The petechiae are from 3 to 35 mm. in diameter and have dark red or purple centers which do not fade on pressure; they develop very rapidly, literally under the observing eye. Clinicians have reported instances of the blotches appearing while the patient is being sponged, while a spinal tap is being performed, while bringing the child to the hospital, and while actually on the admission room table.

Hyperpyrexia is almost universally present; temperatures ranging between 105 and 108° F. are usually the rule although low fevers are occasionally reported. Various investigators report a notable fall in blood pressure readings. This is a direct indication of the tremendous circulatory collapse accompanying the toxemia. In cases where blood pressure readings were not available, some estimation of the amount of shock could be judged by observing the rise in hematocrit readings, the rapid, thready pulse and, terminally, absent radial pulse. The typical picture is that of a fast, weak irregular pulse, shallow respirations, pallor, slowing of the heart rate, and a terminal fall in blood pressure and temperature followed by death within 4 to 48 hours of onset. Most patients with the fulminating type of meningococcemia are admitted to the hospital in a state of shock, with blood pressure readings of from 50 to 80 mm. of mercury or lower, and with purpuric manifestations. It has been suggested that the so-called medical shock induced by the rapid circulatory failure is probably not so much the result of decreased suprarenal secretion but rather a loss of vascular tonicity due to toxic effects accompanying the septicemia.[14]

Associated features occurring as part of the picture of shock are Cheyne-Stokes respiration, urinary incontinence, coma, and delirium. Fleeting signs of pulmonary involvement are not uncommonly seen in quite a few cases. Occasionally, blindness, pains in the extremities, diarrhea, and neurological signs such as muscle flaccidity, tremor, chills, strabismus, convulsions, and rigidity of the abdominal muscles are observed.

Up until the present time, very few reports of recovery have been brought forth. Carey,[5] Bickel,[3] Rucks and Hobson,[25] Sharkey,[26] Peabody,[24] and Grace and associates[11] have each reported a case of recovery from what apparently appeared to be fulminating meningococcemia. But whether the adrenals were

involved cannot be ascertained. The latest report of a recovery from the syndrome is that of D'Agati and Marangoni[8] who presented the case of an 18-year-old soldier. Except for the above mentioned cases, however, the outcome has been uniformly fatal.

It has been suggested that those individuals who have recovered from fulminating meningococcemia be followed in the advent that they should develop some latent complication, such as Addison's disease, of unknown etiology.[28]

Treatment.—Treatment has crystallized into measures aimed at (1) combating the bacteremia and (2) controlling and improving the amount of circulatory collapse with (3) institution of supportive measures. To offset the bacteremia, latest reports advocate the immediate use of sodium sulfadiazine intravenously, followed by the subcutaneous administration of the drug until its use orally is feasible, and until a blood level of 15 mg. per cent has been reached and maintained.[28] In those reported cases in which penicillin has been tried, results were not encouraging, but the opinion of the writers is that a trial of penicillin should be made in a sufficient number of cases before a conclusion can be reached. Antimeningococcic serum, if given at all, should be administered early and in adequate amounts. Circulatory collapse is best combated with adrenal cortical extract and adrenalin. Blood transfusions and vitamin K have been recommended.

Supportive measures include (1) fluids, in the form of 5 per cent glucose with Hartmann's solution, saline, and plasma; (2) respiratory stimulants and aids such as coramine, oxygen, and artificial respiration; (3) sedation for convulsions or delirium when necessary; (4) Wangensteen tube to alleviate abdominal distention if present; and (5) saline enemas.

The following outline of treatment has been suggested[23]:

1. Before any treatment is instituted, samples of blood should be taken for the following laboratory determinations: potassium, sodium, chlorides, nonprotein-nitrogen, carbon-dioxide combining power, sugar, and hematocrit.
2. Aqueous adrenal cortical extract
   a. Immediate intravenous dose as follows:

Weight of patient in kilograms	Dose in cubic centimeters
5	5.0
10	8.0
20	12.0
30	15.0
Adult	25.0 to 40.0

   b. Continuous dose every three hours in conjunction with continuous drip fluid administration:

Weight of patient in kilograms	Dose in cubic centimeters
5	0.5
10	1.0
20	2.0
30	3.0
Adult	5.0 to 10.0

3. Desoxycorticosterone acetate in oil (must be used with caution since overdose produces hemodilution, edema, hypertension, and cardiac failure). It should be given intramuscularly every six to eight hours for three to four doses.

Weight of patient in kilograms	Dose in cubic centimeters
5	0.4
10	0.5
20	1.0
30	2.5
Adult	5.0

4. Sulfonamide drugs in adequate dosage and properly diluted should be administered parenterally by continuous injection.
5. Fluids (5 per cent glucose with normal saline or Hartmann's solution):
   a. Immediate dose of 30 c.c. per kilogram of body weight
   b. Follow at a rate sufficient to give 150 c.c. per kilogram per day.
6. Observe blood pressure every two hours.

Treatment, to be effective, must be started very early in the course of the disease. This is the prime need for a rapid and accurate diagnosis.

Laboratory Findings.—Laboratory findings are not impressively significant. Recovery of the organism from (1) the spinal fluid, (2) the blood by culture, and (3) the petechial hemorrhagic areas constitute the most important laboratory work. Spinal fluid findings are not constant; in many cases the organism cannot even be demonstrated in the fluid nor can definite other findings be noted since the meningitic involvement has not yet become apparent. Thus, cell findings may range from normal (0 to 6 cells) to several thousand per cubic millimeter. Proteins and chlorides may or may not be elevated, while sugar values are usually decreased in the presence of organisms.

Blood findings are also very inconsistent. The organism is often recovered by culture in cases of septicemia. The hemogram may show a leucocytosis ranging as high as 88,000;[22] rarely there is a leucopenia in the presence of overwhelming bacteremia. Differential is noncontributory; there may be either an increase in the lymphocytes or the polymorphonuclear elements. The hematocrit is elevated in proportion to the amount of shock. Bleeding and coagulation times are within normal limits. Urine findings are not significant. Low CO_2 combining power, slightly increased globulin content, and elevated blood nonprotein nitrogen have been reported.[25]

Pathologic Features.—The predominant pathologic feature, and one which is indicative of the syndromal picture, is hemorrhage into the adrenal glands. It has been stated in a review of the literature[25] that bilateral hemorrhage occurs in 95 per cent of cases. The remaining unilateral 5 per cent is nearly always associated with damage to the right adrenal gland. Rucks and Hobson[25] postulate that the frequency of the right adrenal damage is due to (1) greater opportunity for venous stasis through anatomic arrangement of the blood supply (direct opening into the inferior vena cava) and (2) compressed position of the right adrenal between the liver and the spine. In cases of unilateral involvement, the outcome of the disease is usually delayed a few days.

At necropsy, the gross appearance of the glands is described as being almost double the normal size, and dark red or bluish purple; the discoloration can readily be seen through the peritoneum. Medulla and cortex cannot be differentiated on cut section, the entire picture being one of massive intracapsular hemorrhage. No thrombosis, embolism, or inflammation of the glands has been reported.[22] Microscopic sections reveal the destruction of the medulla and zona reticularis together with all but isolated strands of the cortex.

A second important finding is the appearance of an extensive purpuric eruption on the face, extremities, and buttocks. This is believed due to the direct

TABLE I

CASE DATE OF ADM.	AGE SEX RACE	TEMP. ON ADM. °F.	DURATION OF ILLNESS	CLINICAL APPEARANCE AND COURSE OF DISEASE	DIAGNOSIS ON ADMISSION	LABORATORY FINDINGS	TREATMENT	PATHOLOGIC FINDINGS
(1) W. F. 4/28/43	21 mo. male white	105.8	"Few hours"	Obvious shock; convulsions; cyanosis; generalized purpuric rash; rapid, thready pulse Died 2 hr.,17 min. after admission	Circulatory collapse of unknown etiology	Spinal fluid: normal values; culture, meningococcus Blood culture: meningococcus	Coramine; oxygen; caffeine-sodium-benzoate	Bilateral adrenal apoplexy; hyperplasia of thymus; general lymphatic hypertrophy
(2) Z. C. 10/11/43	11 yr. male white	107.8	18 hr.	Extreme prostration; cyanosis; generalized purpura; no radial pulse obtainable Died 4 hr. after admission	Meningococcic meningitis; possible Waterhouse-Friderichsen syndrome	Spinal fluid: cloudy, protein, 60 mg. %; culture and smear, meningococcus I Blood: culture, *Staphylococcus albus*	Sulfadiazine; oxygen; caffeine-sodium-benzoate; enemas	Bilateral adrenal apoplexy; enlarged thymus; generalized visceral purpura
(3) C. F. 4/20/44	26 days female negro	99.2	Undetermined	Cyanosis; coarse râles; purpura over abdomen; rapid, thready pulse Died 1 hr., 10 min. after admission	Fulminating bronchopneumonia; Waterhouse-Friderichsen syndrome	Spinal fluid: culture, meningococcus Blood: culture, *Staphylococcus albus*	Coramine; adrenalin; oxygen	Bilateral adrenal apoplexy; lymphatic hyperplasia; pulmonary atelectasis
(4) D. N. 5/8/44	7 yr. female negro	106.8	Undetermined	Delirium; stupor; vomiting; purpuric rash lymphadenopathy; pulse not obtained; convulsions Died 5 hr., 15 min. after admission	Peripheral circulatory collapse; meningitis	Spinal fluid: culture, negative Blood: culture, negative; hemoglobin, 8.5 Gm.; W. B. C., 15,000; polymorphonuclears, 46%; lymphocytes, 54%	Sulfadiazine; paraldehyde	Bilateral adrenal apoplexy; generalized purpura; pulmonary edema
(5) R. F. 6/5/44	9 mo. male white	Not obtained	3 hr. 45 min.	Fever; rash; shock; purpura; rapid pulse Died 1 hr., 25 min. after admission	Waterhouse-Friderichsen syndrome	Spinal fluid: 965 cells; protein, 80 mg. % Blood: culture, *E. coli*	Coramine; sulfadiazine; oxygen; adrenalin cortical extract	Bilateral adrenal apoplexy; generalized petechiae; pulmonary infarction
(6) E. M. 6/14/44	9 mo. male negro	105.0	14 hr.	Admitted in shock; generalized petechiae Died 1¼ hr. after admission	Waterhouse-Friderichsen syndrome	No data available	No data available	Bilateral adrenal apoplexy; generalized purpura
(7) S. R. 6/28/44	1 yr. female white	101.2	26 hr.	Restlessness; cyanosis; chills; convulsions; purpura Died 7 hr., 50 min. after admission	Waterhouse-Friderichsen syndrome	Spinal fluid: clear Blood: culture, negative; platelets, 45,000; petechial smear, meningococcus	Sulfadiazine; adrenalin cortical extract; coramine; adrenalin	Bilateral adrenal hemorrhage; generalized purpura
(8) E. B. 7/18/44	7 yr. male negro	106.8	12 hr.	History food poisoning; convulsions; delirium; chills; petechiae; coma Died 3 hr., 55 min. after admission	Food poisoning; Waterhouse-Friderichsen syndrome; possible poliomyelitis	Spinal fluid: normal Blood: W.B.C., 3,600; polymorphonuclears, 49%; lymphocytes, 46%; hemoglobin, 10.5 Gm.	Sulfadiazine; phenobarbital	Bilateral adrenal hemorrhage; generalized purpura

involvement of capillaries and arterioles. Petechial hemorrhages may be present in the mucosa of the stomach, intestine, pericardium, pleura, and serosa of the mouth, throat, and bladder.

A fairly constant finding in many cases is a generalized hypertrophy of the lymphatic tissue. The thymus, Peyer's patches, mesenteric glands, and appendix are swollen and enlarged. Pathologic findings indicative of congestion are usually observed. Signs of meningeal irritation are notably absent.

Report of Eight Cases.—Since 1941, at which time the cases of this syndrome occurring at the Children's Hospital were reviewed and reported,[17] eight additional cases of the disease have been collected and are herewith presented. From this series, average age incidence was found to be 44 months; average temperature on admission to the hospital was 104.6° F.; average duration of illness in known instances was about fifteen hours. Admission diagnosis of possible Waterhouse-Friderichsen syndrome was made in six of the eight cases reported. In every case, the pathologic finding of bilateral adrenal hemorrhage was revealed at autopsy. Laboratory findings were extremely variable; meningococci were recovered from both spinal fluid and blood in one-half of the cases. The organisms were recovered in the one instance in which smears were made from the petechial areas.

Table I summarizes the clinical, pathologic, and statistical data.

DISCUSSION

Several theories have been advanced in an attempt to explain the findings in this syndrome.[20] The latest evidence would indicate that the condition is one of overwhelming fulminating meningococcemia producing shock. Peculiar susceptibility of the adrenals to the meningococcus, which has a particular affinity for nervous tissue, is explained on the basis of the embryonic relationship of the adrenal medullary tissue with ectodermic anlage.

Most likely, the entire picture can be explained on the results of the toxemia caused by the widespread bacteremia. The hemorrhages, whether into skin, adrenals, or mucous membranes, are due to the increased permeability of the capillaries and the direct effect of the toxins on the capillary endothelium causing rupture with extravasation. Anatomically, the skin and adrenals are considered to have the most delicate capillary bed; thus, they are probably the first structures to display signs of involvement. One investigator[22] believes the capillaries are blocked by an aggregation of red blood cells and organisms, there being no embolism or abscess.

There is a factor of hepatorenal involvement only recently appreciated which is most apparent in those who survive the initial effects of the bacteremia.[19]

SUMMARY

1. There is an increasing number of cases of the Waterhouse-Friderichsen syndrome in the literature in recent years, probably due both to its more accurate recognition and to the increased incidence of meningococcic infections during the past two years.

2. The condition is believed to be the result of fulminating meningococcemia and shock, and the pathologic findings can be explained on the toxic results of the organisms.

3. Present usage of the term, Waterhouse-Friderichsen syndrome, should be confined to those cases exhibiting the fairly typical clinical course as described, and undoubtedly to those patients whose symptomatology was confirmed

by autopsy. Care should be taken in the early recognition and differentiation of Waterhouse-Friderichsen syndrome from acute meningococcemia.

4. The present outline of treatment centers on control of the bacteremia and measures aimed to combat shock, with secondary symptomatic and supportive treatment.

5. A series of eight cases seen at The Children's Hospital, Washington, D. C., is summarized and presented.

6. All cases presented in this series were in accordance with the clinical and pathologic findings related in the recent literature.

REFERENCES

1. Aegerter, E. E.: J. A. M. A. **106**: 1715, 1936.
2. Banks, H. S., and McCartney, J. E.: Lancet **1**: 771, 1943.
3. Bickel, G.: Rev. méd. de la Suisse Rom. **60**: 1058, 1940.
4. Blaher, P. S., and Bailey, B. E. G.: Brit. M. J., July, 1941.
5. Carey, T. N.: Ann. Int. Med. **13**: 1740, 1943.
6. Cosgriff, S. W.: Ann. Int. Med. **21**: 187, 1944.
7. Cunningham, J. A.: New Zealand M. J. **41**: 238, 1942.
8. D'Agati, V. C., and Marangoni, B. A.: New England J. Med. **232**: 1, 1945.
9. Friderichsen, C.: Jahrb. f. Kinderh. **87**: 109, 1918.
10. Glanzmann, E.: Jahrb. f. Kinderh. **139**: 49, 1933.
11. Grace, W. H., Harrison, C. V., and Davie, T. B.: Lancet **2**: 102, 1940.
12. Herbut, P. A., and Manges, W. E.: Arch. Path. **36**: 413, 1943.
13. Holley, W. J.: Bull. Vancouver M. A. **18**: 276, 1942.
14. Humphrey, A. A., and Toomey, L. O.: U. S. Nav. M. Bull. **42**: 165, 1944.
15. Kunstadter, R. H.: Arch. Pediat. **56**: 489, 1939.
16. Levinson, S. A.: J. Pediat. **14**: 506, 1939.
17. Lindsay, J. W., Rice, E. C., Selinger, M. A., and Robins, L.: Am. J. M. Sc. **201**: 263, 1941.
18. Little, E. G.: Brit. J. Dermat. **1**: 75, 1901.
19. Marangoni, B. A., and D'Agati, V. C.: Am. J. M. Sc. **207**: 385, 1944.
20. Martland, H. S.: Arch. Path. **37**: 147, 1944.
21. Monfort, J. A., and Mehrling, J. H.: Am. J. Dis. Child. **62**: 144, 1941.
22. Morison, J. E.: Lancet **1**: 800, 1943.
23. Park, E. A., Pediatrician-in-Chief, Johns Hopkins: From Files of.
24. Peabody, S. D.: New England J. Med. **229**: 934, 1943.
25. Rucks, W. L., and Hobson, J. J.: J. PEDIAT. **22**: 226, 1943.
26. Sharkey, J.: Lancet **2**: 560, 1941.
27. Thomas, H. M., Jr.: J. A. M. A. **123**: 264, 1943.
28. Thomas, H. M., Jr.: Bull. U. S. Army M. Dept. **73**: 78, 1944.
29. Waterhouse, R.: Lancet **1**: 576, 1911.

OBTURATOR (ACRYLIC) FOR THE NEWBORN INFANT WITH CLEFT PALATE

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THE newborn infant with a cleft palate and often with an associated cleft lip presents a medical problem as well as a surgical problem. Feeding the infant with a cleft palate by medicine dropper or Breck Feeder is time consuming and not without risk of aspiration.

To facilitate the problem of feeding the infant with a cleft palate we first tried the obturator shown in Fig. 1. This has a flexible, flabby rubber flange, which did not close the defect in the palate. Milk returned through the nose and it was very difficult for the baby to take his bottle.

Fig. 1.

Fig. 2.

Fig. 2.

Our first case was that of an infant with a double cleft in the palate and a cleft lip (left), one of twins. The other twin had no visible congenital defects. On the seventh day a model was taken of the baby's palate and maxilla using modeling compound. This modeling compound softens at relatively low temperature and lends itself well to working in the infant's mouth. A satisfactory model was thus obtained and from this model, Cast No. 1 was made. The

Fig. 3.

Fig. 4.

acrylic plate, modeled from Cast No. 1, shown in Fig. 2, was inserted before feedings and removed at the end of each feeding. The nurses who fed the infant reported no difficulty in inserting or removing the obturator. The infant after the second day did not resist the use of the obturator and took his feedings well.

On the fourteenth day the cleft lip shown in Fig. 3 was operated on by Major Joseph Kostrubala, Medical Corps. During the ten-day period following this operation, the obturator was not used so as not to interfere with the healing of the lip. On the twenty-fourth day another model was made of the

baby's mouth (Cast No. 2). Note how much closure in the cleft maxilla took place within ten days following the lip closure. Marked closure was also noted in the cleft palate. At time of writing, the infant was wearing the obturator modeled from Cast No. 2. The formula as well as the cereal feedings were taken without difficulty.

Two months following our first case, a second case of a child born with a cleft palate and a double cleft lip came under our care. This infant (Fig. 4) had a very large defect in the palate. Through this defect the septum and turbinates could be clearly seen. In spite of the large defect in the palate, the acrylic plate fit well and the mother had no difficulty in giving the bottle. Following repair and healing of the lip a second model and plate were made. The obturator was introduced and removed without difficulty and the waste of time required for dropper feeding and the dangers of dropper feeding were entirely eliminated.

In November, 1938, Sillman reported on the use of an obturator made of vulcanite. The acrylic type obturator has some advantages over the vulcanite type. It is lighter in weight, transparent and easier to keep clean, it is entirely tasteless and odorless, absorbs very little or no moisture, thus avoiding any sogginess, extraneous odors, or tastes. It is not irritating to the tissues. Bacteria find a better media for growth on the vulcanite than on the acrylic type obturator. Acrylic is easier to repair and remains transparent after repair.

REFERENCES

1. Sillman, J. H.: Am. J. Dis. Child. 56: 1055, 1938.
2. Sillman, J. H.: Am. J. Orthodontics 24: 409, 1938.
3. Fry, W. K.: Proc. Roy. Soc. Med. 14: 57, 1921.
4. Wearn, W. J.: Austral. J. Den. 34: 423, 1930.

American Academy of Pediatrics

Proceedings

THE PROBLEM OF GOVERNMENTAL-PROFESSIONAL RELATIONSHIPS

(As Seen From Experience Under the EMIC* Program)

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THE pattern of the preceding discussion[1] is peculiarly, and fortunately for me, very much in line with what I had hoped to discuss with you, though I had no advance knowledge of the intentions of the committee which has just submitted its recommendations for your future plans.[2]

I have had the pleasure of working with many of you in person. As a result, I have a strong feeling, in common with a great many people in similar positions, that pediatricians as a group have given evidence of a greater basic social consciousness than most other groups in the medical profession. Today's proceedings have clearly indicated that the Academy is preparing to undertake a new field of leadership. I have no doubt that you are turning over in your minds the question of what the form of this leadership will be.

In the program that you contemplate, your leadership will fall within only one major field of medicine. I hope that you will face the fact that there are over 170,000 physicians in this country, of whom the group here assembled represents only a very small, though influential, portion. If somebody does not undertake responsibility for similar leadership for the profession as a whole, then I rather despair of seeing your efforts or ours accomplish what we all have in mind, namely, the development of a sound national health program in the planning of which physicians themselves will play their proper part.

Recently, in New York, I attended a large meeting of businessmen which was devoted to the consideration of "better medical care for more Americans." The concluding speaker who as an officer of the National Physicians Committee was presented as the spokesman for "organized medicine" made two statements which are important indications of the need for more balanced national thinking or at least expression of it. The first was a definition of adequate medical care which was somewhat as follows: That adequate medical care would be achieved if medical services at the hands of a duly licensed physician were available for everybody. In further comment, quality and facilities were pointedly disregarded. To me, much of medical and social significance is obviously lacking in such a definition. The hospital, the laboratory, nursing care, as well as the need for intimate understanding of and facilities for social adjustments that are inherent parts of medical care, were forgotten. The fact that under our present system medical services are frequently not available for a variety of reasons or when available are often of insufficient quality was disregarded.

Second, he spoke of the many various voluntary medical service plans as the answer to the problem of medical care and expressed the hope that there would be many more of them of various kinds. It is true that such plans are meeting a need. The fact that they are arising, one after another, is a very hopeful sign. Voluntary medical insurance is a step forward because it recognizes a very important principle, but it does not begin to meet the problem of medical care in all of its vastness. So up to a point these medical plans are desirable but eventually, unless properly regarded, they will defeat their purpose by diluting

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interest and dividing effort and attention to the real problem of meeting our national needs. I could not escape the feeling that the speaker recognized this. Surely we must have clearly before us an idea of where we are going, so that we can measure every step that we take as to whether it adds to or detracts from our ultimate objective.

So far, I have disregarded my prepared manuscript and the assignment for which I was brought here, because of the extreme importance of the action you have before you. I hope that as individuals you will carry your progressive and realistic thinking back to your state and county societies.

But allow me to turn to my assignment. Regardless of the temporary nature of the EMIC program, there can be no doubt but that it constitutes an experience in organized medical care on the national plane. It shall be my purpose to review with you some of the conclusions that may be drawn from this experience as they relate to the working relationships between the government and the medical profession. In a sense, those of us who are concerned with this program at the State level are in a favorable position for such analysis because, while we were often squeezed between the regulations of the Federal government on the one hand and opinions of the medical profession on the other, we were, nonetheless, able to catch glimpses of both sides of the problem that are of interest and, I believe, of importance.

My remarks are not intended in a critical sense because, after all, the EMIC program is accomplished; it probably has passed its peak, and review of our past difficulties would serve no purpose if it were not, with the probable future in mind, directed toward a better understanding of the essential elements in governmental-professional relationship.

To begin with, I should like to propose the acceptance of two basic assumptions: First, that we are sincerely interested in the social concept of medicine and are willing to take reasonable measures toward its growth. By the social concept of medicine I mean the concept that it is a responsibility of society to provide for all its members the means for obtaining adequate health and preventive medical services and medical care and that no man shall be deprived of these services by reason of his race, creed, color, or economic status. Second, that inasmuch as we face a period of desirable and inevitable change, it behooves the medical profession to take an active part in the formulation and promotion of such policies as fall within the scope of its particular skill.

I know from considerable experience with pediatricians as individuals and as a group and from the written opinions of members of your specialty, emphasized greatly by your special committee report, that these assumptions are reasonably in line with your views. We need to agree upon the definition of our ultimate objective, and then to develop a broad plan for its achievement. In this connection, I recommend to your study the report and recommendations of the American Public Health Association which are in the process of publication.*

In the matter of basic planning as between the functions of government and the medical profession, there should be much better understanding. I am of the opinion that any national pattern, even where it is national only in its broadest concepts and permits great latitude for regional and local adaptation, will require rather extensive use of the administrative machinery of government. That does not mean, however, that it has to be bureaucratic. Bureaucracy is the product of remoteness. This remoteness may be either geographical or intellectual, or both. I can see no reason why bureaucracy should be a danger in the plans of the future, if the bureaus are reasonably decentralized, as they must be, and if they are supported by the intelligent cooperation of the medical profession and if the persons concerned with their administration at the various levels will take the trouble to get acquainted.

The problems attending the provision of medical care on a national or local basis encompass three major areas: (1) the economic aspects of medical care, (2) the quality of medical care, and (3) the equitable distribution of medical care.

While the medical profession cannot help but be interested in and, to some extent, concerned with the economic problem, it must recognize that government owes a far greater responsibility in this matter to the total population of 130 million than it does to the relatively small segment of the total population which physicians and their families constitute. In solving this economic problem, as with any other, therefore, the government will be obliged to consider the attitudes and opinions of many groups and the weight of the medical profession in a direct sense cannot be expected to be very great, other than to the extent that it should expect reasonable protection of the economic interests of physicians as a matter of fair policy.

*Am. J. Pub. Health 34: 1252, 1944.

The EMIC program provides materials very much to the point. The organized medical profession made vigorous attempts to introduce the principle of cash allotments for the wives of servicemen rather than payment for services directly to the physician and hospital. In many ways this would have been most satisfactory to the physicians concerned and I can assure you it would have been the simplest, though not necessarily the most desirable, solution from the point of view of the administering agencies. However, Congress, representing the 130 million, took a broader view toward the government's responsibilities and insisted upon the inclusion of provisions that would, in so far as possible, protect the quality and extent of medical care that the soldiers' wives and families received and guarantee that the funds allocated for this purpose would be properly used.

However, when the details of planning concerning the quality and the equitable distribution of medical services are under consideration, the government must turn to those with technical knowledge and experience and should be able to expect the cooperation of the professions concerned. As a matter of fact, I would go so far as to say that in respect to these particular phases of the problem we might consider that the medical profession has the primary responsibility and that it should use the agency of government, which the nation, in a sense, has placed at its disposal, in the confidence that it will thereby be able to make provision for better medical care for everybody.

During the past three years I have had the privilege of intimate discussion both with government officials and with leaders in the medical profession. I have sat in or participated at numerous conferences with government agencies, the medical profession, and in joint conferences. As an observer it seems to me that serious mistakes have been made on all sides. The government agency may not, for one reason or another, have been able, or perhaps entirely willing, to seek the advice of the medical profession in the early stages of its planning. But perhaps the government agency has not been entirely to blame, because the medical profession, as an organized body, has either not presented a suitable organizational structure for this purpose or has been reluctant, possibly unable, to undertake the type of negotiating conference that the situation required.

As Dr. Wall[2] has mentioned, the Children's Bureau finally, and in my opinion belatedly, invited official representation of organized medicine and other groups to a planning and discussion conference a little less than a year ago. But what possible good could be expected to result under circumstances where the representatives attending that conference in behalf of the American Medical Association evidently were under specific instructions to reopen the question of a cash allotment which had already been turned down by Congress and the medical representatives knew this? At the meeting in question many other topics of importance were discussed but I was deeply disappointed with the inability of the medical representatives present to seize that opportunity to establish with the Children's Bureau a practical working relationship in which points of view and problems could be discussed fully and in which those present could direct themselves to the working out of a satisfactory solution.

What if compromise were the price? I am unable to see how anyone can expect us to move intelligently as a nation in reconciling the divergent points of view which we are bound to encounter unless a basis for discussion and negotiation among responsible persons can be established. The need for power to negotiate in behalf of groups is not exclusively one of international affairs.

I am happy to be able to comment at this point that the representatives of the pediatric profession were able to and did take a much more constructive position and seemed willing to discuss the problems with a view to helping the Children's Bureau to reach the decisions that it had to make. Whether this was done by them as individuals or as official spokesmen of this Academy I do not know. The meeting was too large and it was sometimes difficult to know in exactly what capacity those present were speaking.

In New York State at the present time we feel ourselves to be in a somewhat more fortunate position. I cannot speak for other states, though I suspect that our experience is no longer unique. In fact, our experience today is quite different than it would have been some years ago. In any event, the very first move made by the Commissioner of Health in the spring of 1942, when he was presented by the Children's Bureau with the proposal for the Federal EMIC program, was to place the matter before a working committee of the Council of the New York State Medical Society and its Subcommittees on Maternal and Child Welfare. The Child Welfare Subcommittee, incidentally, is composed of members of the American Academy of Pediatrics and includes the State chairmen both for the upstate New York area and New York City.

Possibly the members of that subcommittee who are present today will wish to take exception to what I have to say, but I do not believe they will. I feel that despite the

difficulties of the EMIC program and the criticism of the Department of Health and its individual administrators that it evoked, which occasionally reached the height of vindictiveness, and despite the other stresses and strains of this very difficult period, we have emerged with a closer mutual working relationship and even better understanding than we had before.

Of course, in this instance, we were dealing with a Federal program and with regulations not of our own making for the most part. In a sense the Department of Health acted as the arbiter between the physicians in New York State and the Children's Bureau. What part our efforts played in the ultimate modification of many of the early features of the plan, I cannot say. I am sure that other factors, states, and groups, such as the American Academy of Pediatrics, were at work, not the least of which was a willingness on the part of the Children's Bureau to listen to the problems of those with the direct responsibility for the program at the operating level. Possibly we, by reason of the years of our association with the Children's Bureau, had a better negotiating understanding.

Despite its final outcome and the fine working relationships involved, I do not believe that the manner in which this was handled should be considered as a desirable pattern for future planning. How, for example, could the Children's Bureau be expected to negotiate with the medical profession through fifty-one intermediary health agencies presenting, probably, fifty-one different shades of medical opinion thoroughly mixed, for the most part, with their own views?

The real test of the working relationship in New York State that I have cited is not in the function of arbitrating between Federal regulations and medical opinion but rather in the manner of developing plans and the administration of programs that originate at the State level. I believe that we have had sufficient experience with this type of working relationship to know that it can be done where a given activity is definitely a state responsibility.

The department is accustomed to presenting its views to these representatives of the medical profession and to accepting modifications and adjustments in so far as they are within the intent of legislation and administrative wisdom. Where such adjustments cannot be brought about, we are accustomed to frank discussion of the reasons. And, though I am glad to say such instances are extremely rare, we invariably meet with understanding. Furthermore, the long-range objectives of any program that the department undertakes and the thinking and personalities of its administrators are known to these representatives of medicine. Like all groups that work together closely, we inevitably formulate ideas and mutual plans in the process of such association.

It should be possible to translate the type of experience which I have described at the state level to its Federal counterpart, but it requires a determination to make it succeed on both sides.

With respect to the importance of operating Federal agencies, I should like to comment briefly. Congress, if I am not mistaken, in common with most legislative bodies, has a tendency to be a bit unpredictable. However, I am sure that the degree of scattered congressional activity and discussion in any given field varies in more or less inverse proportion to the strength and soundness of the corresponding Federal agency or agencies. By that I mean that, if Congress knows that there is an agency in Washington that works closely with all of the professions in the field of medical care and is sensitive to the other important relationships, it is logical to assume that they will pay a great deal more attention to the opinions of that agency and will be more likely to direct their thinking along lines of organized national planning than they otherwise could do. Hence, I believe that strong, well-selected Federal agencies should be built and supported—not destroyed—and that good medical men should staff them. They can be a friend to us and our objectives.

I feel deeply the privilege, the responsibilities, and opportunity provided by your kind invitation to participate in this symposium. Because I feel as I do, I have spoken rather directly.

The time really is short. Opportunities for making sound and thoroughly desirable progress in the social concept of medical care are at every hand.

I have spoken critically of the manner in which the medical profession has proceeded and equally of the Federal agency. I have also spoken well of both—that is not hard because I have a high regard for both. But, as a physician and as a medical administrator in government, I lay before you a somewhat impassioned plea. I am absolutely convinced that substantial progress cannot be made by widening the breach between the medical profession and government. Those of us who are trying to steer the future course along sound lines require your understanding and your help. In return we can offer the support and strength to your objectives of properly operating government.

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1. Wall, Joseph S.: J. PEDIAT. 26: 89, 1945.
2. Report of Committee on a Consideration of Child Health in the Postwar Period: J. PEDIAT. 25: 625, 1944.

Report of the Committee on Geographical Distribution of Pediatricians

Charts I to IV were a part of the Report of the Committee on Geographical Distribution of Pediatricians presented at the Meeting of the Executive Board of the American Academy of Pediatrics, Chicago, Ill., June 15 and 16, 1945. The Committee report was published in the August issue of the JOURNAL, page 189.

These charts, showing the distribution and changes in physicians by States between 1937 and 1942, the number of Academy Fellows in each state, and the number of Diplomates of the American Board of Pediatrics, were prepared by Dr. Otto L. Goehle, Academy Committee on Geographical Distribution of Pediatricians.

CHART I. REGION I (EAST); CHART SHOWING DISTRIBUTION OF INCREASE PER STATE; TOTAL INCREASE FOR REGION I

STATES	POPULATION (1937)	POPULATION (1942)	INCREASE IN POPULATION	TOTAL NO. OF PHYSICIANS (1937)	TOTAL NO. OF PHYSICIANS (1942)	INCREASE NO. OF PHYSICIANS	TOTAL NO. OF F.A.A.P. (1937)	TOTAL NO. OF F.A.A.P. (1945)	INCREASE NO. OF F.A.A.P.	TOTAL NO. DIPLOMATES (1937)	TOTAL NO. DIPLOMATES (1942)	INCREASE NO. OF DIPLOMATES
Connecticut	1,655,000	1,709,242	54,242	2,401	2,720	321	42	56	14	36	49	13
Delaware	242,000	266,505	24,505	316	360	44	4	6	2	2	6	4
District of Columbia	497,000	796,000	299,000	1,979	4,540	2,561	32	32	0	14	35	21
Maine	804,000	847,226	43,226	966	1,011	45	5	6	1	0	1	1
Maryland	1,671,000	1,821,244	150,244	2,730	3,085	355	20	25	5	12	21	9
Massachusetts	4,335,000	4,316,721	18,279	7,263	8,085	822	56	75	19	65	83	18
New Hampshire	470,000	491,524	21,525	593	687	94	2	6	4	1	5	4
New Jersey	4,231,000	4,160,165	70,835	5,177	6,008	891	48	70	22	39	51	12
New York	13,059,000	13,479,142	420,142	24,013	27,928	3,915	196	282	86	274	368	94
Pennsylvania	9,826,000	9,900,100	74,100	12,889	13,503	614	79	110	31	69	107	38
Rhode Island	705,000	713,346	8,346	924	958	34	12	13	1	4	8	4
Vermont	361,000	359,231	1,769	503	551	48	2	6	4	2	4	2
Grand Total	37,856,000	38,860,446	1,002,446				498	687	189 (37.9+% increase)	518	738	220

CHART II. REGION II; (SOUTH) CHART SHOWING DISTRIBUTION OF INCREASE PER STATE; TOTAL FOR REGION II

STATES	POPULATION (1937)	POPULATION (1942)	INCREASE IN POPULATION	TOTAL NO. OF PHYSICIANS (1937)	TOTAL NO. OF PHYSICIANS (1942)	INCREASE NO. OF PHYSICIANS	TOTAL NO. OF F.A.A.P. (1937)	TOTAL NO. OF F.A.A.P. (1945)	INCREASE NO. OF F.A.A.P.	TOTAL NO. DIPLOMATES (1937)	TOTAL NO. DIPLOMATES (1942)	INCREASE NO. OF DIPLOMATES
Alabama	2,710,000	2,832,961	122,961	2,105	2,123	18	15	21	6	11	16	5
Arkansas	1,876,000	1,949,387	73,387	1,911	1,866	45	4	4	0	1	3	2
Florida	1,575,000	1,897,414	322,414	1,939	2,391	352	21	26	5	13	21	8
Georgia	2,911,000	3,123,723	212,723	2,765	2,841	76	19	33	14	25	33	8
Kentucky	2,657,000	2,845,627	188,627	2,770	2,717	53	12	16	4	10	18	8
Louisiana	2,166,000	2,363,880	197,880	2,135	2,601	466	18	27	9	11	15	4
Mississippi	2,057,000	2,183,796	126,796	1,515	1,525	10	6	11	5	7	9	2
N. Carolina	3,301,000	3,571,623	270,623	2,570	2,871	301	20	24	4	25	30	5
Oklahoma	2,475,000	2,336,434	138,566	2,380	2,284	96	11	14	3	12	13	1
S. Carolina	1,750,000	1,899,804	149,804	1,335	1,427	92	8	11	3	11	14	3
Tennessee	2,676,000	2,915,341	239,841	2,939	2,961	22	26	31	5	26	35	9
Texas	6,073,000	6,414,824	341,824	6,729	6,952	223	52	76	24	44	70	26
Virginia	2,446,000	2,677,773	231,773	2,734	2,920	186	19	31	12	20	29	9
West Virginia	1,786,000	1,901,974	115,974	1,792	1,834	42	10	9	1	6	10	4
Grand Total	36,459,000	38,915,061	3,356,061				241	334	93 (38.5+% increase)	222	316	94

CHART III. REGION III (MIDWEST); CHART SHOWING DISTRIBUTION OF INCREASE PER STATE; TOTAL FOR REGION III

STATES	POPULATION (1937)	POPULATION (1942)	INCREASE IN POPULATION	TOTAL NO. OF PHYSICIANS (1937)	TOTAL NO. OF PHYSICIANS (1942)	INCREASE NO. OF PHYSICIANS	TOTAL NO. OF F.A.A.P. (1937)	TOTAL NO. OF F.A.A.P. (1945)	INCREASE NO. OF F.A.A.P.	TOTAL NO. DIPLOMATES (1937)	TOTAL NO. DIPLOMATES (1942)	INCREASE NO. OF DIPLOMATES
Colorado	1,069,000	1,123,296	54,296	1,933	1,886	47	11	16	5	14	22	8
Illinois	7,863,000	7,897,241	34,241	11,672	12,548	876	100	126	26	92	144	52
Indiana	3,467,000	3,427,796	39,204	4,025	4,165	140	17	20	3	16	20	4
Iowa	2,548,000	2,538,268	9,732	3,146	3,102	44	12	14	2	16	17	1
Kansas	1,874,000	1,801,028	72,972	2,188	2,042	146	7	8	1	1	4	3
Michigan	4,808,000	5,256,106	448,106	5,865	6,509	644	46	79	33	61	78	17
Minnesota	2,644,000	2,792,300	148,300	3,283	3,614	331	26	33	7	33	40	7
Missouri	3,975,000	3,784,664	190,336	5,496	5,183	313	23	38	15	10	44	13
Nebraska	1,364,000	1,315,834	48,166	1,781	1,637	144	8	13	5	10	12	2
North Dakota	705,000	641,935	63,065	526	520	6	3	3	0	1	3	2
Ohio	6,724,000	6,907,612	183,612	8,907	9,406	499	79	88	9	74	99	25
South Dakota	692,000	642,961	49,039	562	493	69	2	2	0	2	2	0
Wisconsin	2,918,000	3,137,587	219,587	3,387	3,551	164	15	18	3	10	13	3
Total	40,651,000	41,266,628	615,628				349	458	109 (31.2+% increase)	361	498	137

CHART IV. REGION IV (WEST); CHART SHOWING DISTRIBUTION OF INCREASE PER STATE; TOTAL FOR REGION IV

STATES	POPULATION (1937)	POPULATION (1942)	INCREASE IN POPULATION	TOTAL NO. OF PHYSICIANS (1937)	TOTAL NO. OF PHYSICIANS (1942)	INCREASE NO. OF PHYSICIANS	TOTAL NO. OF F.A.A.P. (1937)	TOTAL NO. OF F.A.A.P. (1945)	INCREASE NO. OF F.A.A.P.	TOTAL NO. DIPLOMATES (1937)	TOTAL NO. DIPLOMATES (1942)	INCREASE NO. OF DIPLOMATES
Arizona	409,000	499,261	90,261	520	615	95	5	6	1	3	5	2
California	6,110,000	6,907,387	797,387	10,859	12,865	2,006	98	128	30	89	111	22
Idaho	489,000	524,873	35,873	410	446	36	2	3	1	1	2	1
Montana	535,000	559,456	24,456	483	556	73	2	4	2	1	2	1
Nevada	101,000	110,247	9,247	149	174	25	2	2	0	0	1	1
New Mexico	422,000	531,816	109,816	401	447	46	4	4	0	2	3	1
Oregon	1,022,000	1,089,684	67,684	1,344	1,493	149	5	8	3	8	10	2
Utah	518,000	550,310	32,310	543	585	42	2	8	6	2	4	2
Washington	1,651,000	1,736,191	85,191	2,049	2,234	185	15	19	4	13	20	7
Wyoming	234,000	250,742	16,742	261	263	2	1	1	0	0	2	2
Total	11,491,000	12,759,967	1,268,967				136	183	47 (34.6+% increase)	119	159	40

News and Notes

The Pediatric Section of the Kings County Medical Society of Brooklyn, N. Y., announces the re-election of its present officers for another year. They are Dr. Abraham M. Litvak, president, Dr. Henry Rascoff, vice-president, Dr. Harold Levy, secretary, and Dr. Samuel K. Levy, treasurer.

Dr. James L. Winemiller, 24 Wensley Drive, Great Neck, N. Y., died Oct. 1, 1944.

The Pediatrician and the War

The following Fellows of the Academy elected at the June meeting of the Executive Board are serving with the Armed Forces:

Army

Dr. Fred Harold Allen, Jr., Holyoke, Mass. (Captain)
Dr. Franklin A. Benes, Shaker Heights, Ohio (Captain)
Dr. William V. B. Deering, Chicago, Ill. (Captain)
Dr. Ernest Freshman, Oneida, N. Y. (Captain)
Dr. Frank D. Hazlett, Washington, Pa. (Major)
Dr. Martin J. Hurst, Kansas City, Mo. (Captain)
Dr. Maurice W. Laufer, Yellow Springs, Ohio (First Lieutenant)
Dr. Jacob J. Lichterman, Brooklyn, N. Y. (Captain)
Dr. John Fleck Miller, Newark, Ohio (Major)
Dr. Edward B. Plattner, University City, Mo. (First Lieutenant)
Dr. Herman Schneck, New York, N. Y. (Captain)
Dr. Irving Silverman, Boston, Mass. (Captain)
Dr. Joe M. Strayhorn, Nashville, Tenn. (Major)

Navy

Dr. Robert A. McGuigan, Evanston, Ill. (Lieutenant Commander)

United States Public Health Service

Dr. Daniel C. Hackett, Rochester, N. Y.

It is reported in *The Journal of the American Medical Association* that Captain Herman Schneck of New York City has been commended for "superior performance of duty and maintenance of medical facilities."

The following Fellows of the American Academy of Pediatrics have been promoted:

Army

Captain Harry O. Davidson, Detroit, Mich., to Major
Major Frank H. Douglass, Seattle, Wash., to Lieutenant Colonel
Lieutenant Colonel James G. Hughes, Memphis, Tenn., to Colonel
Major Winfred P. Killingsworth, Port Arthur, Texas, to Lieutenant Colonel

The following discharges from service have been reported:

Dr. Herbert C. Archibald, Oakland, Calif.
Dr. Robert M. Finks, San Angelo, Texas
Dr. A. K. Geddes, Montreal, Canada
Dr. Edward A. Hagmann, Billings, Mont.
Dr. Jack E. Strange, New Orleans, La.